Epidemiology of Pneumococcal Disease in Scotland

Implications for vaccine prevention policies and strategies

Moe Hein Kyaw

A thesis submitted for the Doctor of Philosophy

University of Edinburgh 2002

Declaration of Work

I, Moe Hein Kyaw, declare that the contents of this thesis are my own work unless acknowledged otherwise.

Moe Hein Kyaw

Date: 15 July 2002

ACKNOWLEDGEMENTS

The studies in this report were performed during my research training at the Scottish Centre for Infection and Environmental Health (SCIEH) in Glasgow, Scotland, from 1999 to 2002. It was impossible to complete these studies without the help, assistance and advice from many people.

I would like to express special thanks to my mentors Harry Campbell and Ian G Jones for their guidance, encouragement and support, which are fundamental for the completion of the studies. I learned a great deal from them.

I am grateful to all the staff at SCIEH for their friendship and contribution to the studies, in particular to Beverly Wayne, Catherine Speirs, Patricia Cassels, Mark Getty and Stuart Adams for data management involving sending questionnaires for the surveys and data entry for the studies and Eileen Holmes for statistical advice, performing Mann-Whitney tests and Kruskal-Wallis tests for the survey of pneumococcal polysaccharide vaccine use in nursing homes and random sample selection of hospital doctors for the survey of pneumococcal polysaccharide vaccination practices in general practitioners and hospital doctors. I am very grateful to Lesley Wallace, Norman McDonald, Johanna Reilly, Ellen Carragher and Susan Jardine for their valuable comments on this thesis. I would also like to thank Peter Christie for helpful discussions and clarification of issues in relation to infectious disease surveillance systems in Scotland. I also thank Marian Martin for her extensive help in formatting the questionnaire surveys, designing a poster for the record linkage study and a PDF version of this thesis.

I would also like to thank all the staff at the Scottish Meningococcus and Pneumococcus Reference Laboratory for their hard work in the national surveillance of meningococcal and pneumococcal disease and for contributing laboratory data on these diseases. I am in particularly grateful to Stuart Clarke and Barbara Denham for their advice and clarification of laboratory data.

I am indebted to the following staff at the Information and Statistics Division of the Common Services Agency (ISD) and the Scottish Executive: Jim Chalmers, Matthew Armstrong, James McNally, Ann Mochrie, Lynn Forest, Bill Gold, Kevin Pearson, Kenny McIntyre and Jean Goldie for those parts of study data involving prescriptions of antibiotics and pneumococcal polysaccharide vaccine, and the identification of high-risk patients in Continuous Morbidity Recording (CMR) practices.

Finally, I acknowledge financial support from the Chief Scientist Office of the Scottish Executive Health Department for the survey "Pneumococcal vaccine immunisation of high-risk adults in Scotland: an evaluation of vaccine utilisation in primary care and hospital care".

TABLE OF CONTENTS

ABSTRACT

Background: Pneumococcal disease is an important cause of hospitalisations and death in the UK. In addition, antibiotic resistant pneumococci are a problem in several countries. Data on coverage of pneumococcal polysaccharide vaccine and the factors associated with its use are poorly understood in the UK. This thesis investigates the epidemiological characteristics of pneumococcal disease and pneumococcal polysaccharide vaccination practices in Scotland.

Methods: Laboratory data collected through a national network of diagnostic laboratories covering the entire population of Scotland was reviewed to examine the epidemiological characteristics of pneumococcal disease. Cross-sectional surveys were conducted to explore pneumococcal polysaccharide vaccination practices.

Results: The incidence of invasive pneumococcal disease is highest in young children aged less than 2 years ($44.9/10^5$ persons) and in the elderly aged 65 years and above ($28.4/10^5$ persons). The incidence of pneumococcal meningitis is highest in children aged less than 2 years ($11.8/10^5$ persons). There was a 3-fold increase in the prevalence of penicillin (from 4.2% to 12.6%) and erythromycin (from 5.6% to 16.3%) non-susceptible pneumococcal isolates over the study period 1988 to 1999. Regional differences in the prevalence of antibiotic non-susceptibile pneumococci correlated weakly with the rate of penicillin prescription, but not with erythromycin prescription. Pneumococci are the leading cause of invasive non-meningeal bacterial disease and the second leading cause

of bacterial meningitis in Scotland after introduction of Hib conjugate vaccine in the national vaccination programme.

The formulation of current pneumococcal polysaccharide vaccine covers the serotypes responsible for the majority of invasive and non-invasive disease in Scotland. Coverage of invasive and non-invasive serotypes by pneumococcal conjugate vaccines was substantially higher in younger age groups (5 years and less) than in older age groups. All polysaccharide and conjugate pneumococcal vaccines cover nearly all serotypes associated with invasive and non-invasive resistant pneumococcal disease.

General practitioners and hospital doctors have an adequate knowledge of pneumococcal polysaccharide vaccination. However, coverage of pneumococcal polysaccharide vaccine was only 13% among the high-risk patients who are currently recommended to receive this vaccine by the UK Departments of Health. The use of pneumococcal polysaccharide vaccine has increased over the period 1996 to 1999. The majority of pneumococcal polysaccharide vaccination was carried out in general practice (94%) and the remainder were in homes (4%) and in hospital settings (2%).

Recommendation from primary care teams was the principal reason for receipt of the vaccine. Doctors considered that the most appropriate strategies to increase the coverage of pneumococcal polysaccharide vaccine were clear national recommendations, reimbursement policies, computerised systems to identify high-risk patients and professional education, coupled to a national campaign for vaccination.

Conclusions: Pneumococcal disease poses a substantial public health burden in Scotland. The formulation of current pneumococcal polysaccharide and conjugate vaccines includes the most prevalent serotypes associated with disease and antibiotic resistance in young children and adults. Improved strategies such as clear immunisation policies and financial support for vaccination as identified in this study, could improve the delivery and coverage of pneumococcal polysaccharide vaccine in high-risk groups.

ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
CAP	Community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CMR	Continuous morbidity recording
CSF	Cerebrospinal fluid
DoH	Department of Health
GP	General practitioners
HARRT	Highly active antiretroviral therapy
HB	Health Board
HD	Hospital doctor
HIV	Human immunodeficiency virus
INMD	Invasive non-meningitic disease
IPD	Invasive pneumococcal disease
ISD	Information and Statistics Division
MIC	Minimum inhibitory concentrations
MLEE	Multilocus enzyme electrophoresis
MLST	Multilocus sequence typing
NHS	National Health Service
NIPD	Non-invasive pneumococcal disease
NPC	Nasopharygeal carriage

OM	Otitis media
PCV	Pneumococcal conjuagte vaccine
PPV	Pneumococcal polysaccharide vaccine
PR	Penicillin resistance
RCT	Randomised controlled trial
RSV	Respiratory syncytial virus
SCIEH	Scottish Centre for Infection and Environmental Health
SMPRL	Scottish Meningococcus and Pneumococcus Reference Laboratory
UK	United Kingdom
URTI	Upper Respiratory Tract Infection
US	United States
WHO	World Health Organisation

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

The burden of pneumococcal disease

The bacterial pathogen, *Streptococcus pneumoniae* (the pneumococcus) is an important cause of morbidity and mortality in Scotland and worldwide. It is the most common cause of bacteraemia, meningitis, pneumonia, otitis media and sinusitis and affects particularly young children, the elderly and persons with certain underlying conditions, which place them at increased risk.[1,2] The pneumococcus has the potential to cause outbreaks or epidemics in crowded settings.[3] In addition, many diseases caused by it could be considered as endemic throughout the world.[4] On a global level, the pneumococcus is responsible for 1.2 million deaths each year in children under five years of age.[5] No estimated figures are available for death in adults and the elderly.

Despite the use of antimicrobial agents, case-fatality rates of IPD ranged 12-38%.[6-8] Although penicillin has historically been the antibiotic of choice for treating pneumococcal disease, pneumococcal resistance to penicillin and other antimicrobial agents is increasing globally.[9,10] Recent studies have documented that penicillin resistant invasive pneumococcal strains are associated with adverse medical outcomes.[6,8] This has implications for both the choice of antibiotics and the cost of managing pneumococcal disease, particularly meningitis.[11]

These data emphasise the need to prevent pneumococcal disease and minimise the impact of antibiotic resistance through vaccination.

Prevention of pneumococcal disease

Currently, polysaccharide and conjugate vaccines are available for the prevention of pneumococcal disease. The 23-valent pneumococcal polysaccharide vaccine (PPV) is safe, and is effective in preventing 50-80% of invasive pneumococcal disease (IPD) in older children and adults[1,12] (section: 1.2). However, its use for the prevention of non-bacteraemic pneumococcal pneumonia is controversial due to inconclusive evidence from clinical trials in adults.[12] The vaccine is currently recommended for those aged two years and above with certain medical conditions (Table 15). However, vaccine coverage is poor among recommended groups in the UK[13,14] and most other developed countries,[15] indicating low acceptance of PPV among clinicians and patients.

PPV is generally ineffective in children under two years, the age group with the highest risk of pneumococcal disease. This has led to the development of pneumococcal conjugate vaccines (PCV), which include the 7 to 11 serotypes causing most disease in young children worldwide. A licensed 7-valent conjugate has been shown to be 97.4% effective against invasive disease[16] and 56-57% against otitis media[17,18] caused by the vaccine serotypes. The available evidence also indicates that conjugate vaccine has the potential to reduce the incidence of pneumonia, otitis media and lower and upper respiratory infections.[16,19] Pneumococcal conjugate vaccines are safe and immunogenic in the elderly and those with immunocompromised conditions such as HIV, Hodgkin's disease, sickle cell disease, compared with the polysaccharide vaccine.[20] These data suggest that PCV raises the very real prospect of preventing pneumococcal disease in children and high-risk groups. A 7-valent vaccine, known as Prevenar, has now obtained licensure in the UK and most parts of Europe. This vaccine has already been included in the routine childhood immunisation schedule in the US.[2] The UK Joint Committee on Vaccination and Immunisation has now recommended that PCV should be given to children less than two years of age with certain high-risk conditions.[21] A decision on the inclusion of the vaccine into the UK primary immunisation programme is expected soon.

Other preventive measures include prophylactic antibiotics for persons with immunocompromised conditions and changes in environmental or life-style factors in areas with high rates of disease.

Research needs

In Scotland, little is known about the magnitude of the disease burden, the prevalence of antibiotic resistance, which serotypes are associated with disease and the distribution and utilisation of the current polysaccharide vaccine. Obtaining these data are vital for developing and guiding immunisation policy for both polysaccharide and conjugate vaccines. These data will also be useful in assessing the direct and indirect impact of conjugate vaccine on pneumococcal disease after its incorporation into the UK primary immunisation programme.

This thesis investigates the burden and epidemiology of pneumococcal disease and the characteristics of immunisation practices with PPV in Scotland.

1. REVIEW OF THE LITERATURE

1.1. Pneumococcal disease epidemiology

1.1.1. The pneumococcus

1.1.1.1. Organism

The pneumococcus is an encapsulated gram-positive bacterium. It has three main surface layers: plasma membrane, cell wall and capsule.[22] The polysaccharide capsule is the thickest layer of the organism and completely covers the inner components.[23] It protects the bacterium from phagocytosis.[24] Ninety serotypes have been identified based on antigenic differences in the capsular polysaccharide.[25] Serotypes with similar chemical properties are defined as serogroup (e.g. serotypes 9N and 9V in serogroup 9). There are a total of 45 serogroups. It is generally acknowledged that there is some degree of cross-protection for serotypes within one serogroup. The extent of invasiveness depends on the chemical composition of the capsular polysaccharide which differs among serotypes.[26,27] This presents a considerable challenge when developing an optimal pneumococcal vaccine.

The pneumococcccus is transmitted from person to person through respiratory droplets or "autoinoculation" in persons carrying the bacteria in their upper respiratory tract.[28] Studies have shown that susceptibility to pneumococcal disease is determined by the ability of the host to generate specific opsonising antibodies against capsular antigens.[29,30] However, the pneumococcus has the ability to escape ingestion and destroy host phagocytic cells and subsequently cause disease.[28] Molecular and cellular biological studies have demonstrated that the pneumococcus can transfer capsular genes from one strain to another leading to a change in capsular specificity.[31,32] This has important implications for PCV use in the future.

1.1.1.2. Nasopharyngeal carriage

The mucosal epithelium of the nasopharynx is the primary site of pneumococcal colonisation.[24] Risk factors associated with colonisation include young age, overcrowding, day care attendance, siblings attending day care, breast-feeding, winter season, parental smoking, antibiotic treatment and concurrent of upper respiratory infection.[33]

The prevalence of nasopharygeal carriage (NPC) is up to 60% in pre-school children, 25-35% in high school students, 18-29% in adults with children in the household, and 6% in adults without children in the household.[34] The rate of carriage can be as high as 97% in children who live in institutions or attend day care.[35,36] Thus, it appears that children are likely to be the major source of transmission in the family. Intense and early exposure to pneumococci is common in children in native populations and developing countries, with reported carriage rates of 60-89%.[37-43] Evidence of simultaneous carriage of three to five different serotypes has been reported.[44-46] It has been suggested that the number of multiply colonised children is likely to be higher than previous reports because of the lack of a sensitive assay to detect simultaneous carriage of multiple colonisation.[46] A reliable method to detect carriage of multiple serotypes is particularly important when assessing the impact of PCVs on NPC.

Colonisation commonly occurs at some point during the first two years of life in most children.[47-50] More than 95% of children are sequentially colonised with as many as six different serotypes during that time.[51] Carriage rates gradually increase from 9% to 43% from two to 24 months of age[52] and then decrease between three and five years of age.[35,53,54] The duration of nasopharyngeal carriage varies with the age of child[51] and the serotype.[55] The median duration of carriage is 30 days in those under one year, 21 days in those between one and four, 13 days in those aged five to six, and 14 to 15 days in the age group 7 and above.[55] However, little is known about the kinetics of acquisition and the clonal diversity and transmission of pneumococcal isolates in the community and in children.

Nasopharyngeal colonisation occurs as a result of interaction between pneumococcal surface proteins and surface cell receptors.[56,57] The occurrence of acute otitis media (OM),[36,58] bacteraemia[41,59,60] and pneumonia[61] is associated with nasopharyngeal colonisation,[36,43,62] either by haematogenous spread or direct extension.[63] This suggests that nasopharyngeal colonisation is an important risk factor for disease development. Studies have also shown that carriage serotypes are comparable to serotypes responsible for invasive disease and antibiotic resistance[60,62,64,65] and otitis media.[58,66,67] The risk of developing disease from carriage is greatest in the first month following colonisation with a new serotype,[51] with up to 76% of disease occurring during this period.

1.1.1.3. Serotype distribution

Serotype distribution varies with age, type of specimen, geographical location, antimicrobial resistance and time.[68-70] There have been no observed variations in the prevalence of common serotypes according to gender or racial group.[71] Currently, 5 to 8 and 10 to 11 serotypes are responsible for at least 75% of IPD in children and older children/adults respectively, worldwide.[72] Serotype 1 is more frequently isolated from blood, serotype 3 from middle ear fluid and serotype 8 from CSF.[72] The evidence suggests that pneumococcal vaccine effectiveness is dependent on the distribution of vaccine serotypes circulation in the population.[69] Therefore, a knowledge of local serotype distribution is vital in determining vaccination policy.

Serotypes 1, 2, 3, 18C were the most prevalent during 1950s in Europe and the US, accounting for up to 75% of bacteraemic disease.[35,73,74] Serotypes 6, 14, 18 and 19 are to date the most common cause of invasive and non-invasive disease in the UK,[75-77] other European countries[72,78] and the US.[68] An extensive analysis of 70 datasets worldwide found that serotypes 4, 6, 9, 14, 18, 19 and 23 caused 70-88% of IPD in young children in Europe, North America and Oceania.[72] In addition to these, serotypes 1, 5, 3 and 7 are major causes of IPD in adults in both developed and developing countries.[72]

Serotypes 3, 19 and 23 are more commonly isolated from middle ear fluid among young children in Europe and North America.[78]

The most common serotypes associated with IPD among children in developing countries are, in decending order, 6, 14, 8, 5, 1, 19, 9, 23, 18, 15 and 7.[69] Serotypes 1 and 5 are the most prevalent causes of IPD in young children[69,72] accounting for 15% to 20% of IPD in Latin America, Asia and Africa.[72] They are also responsible for as much as 25% in older children and adults in Asia.[72] The reasons for the differences in serotype distribution between countries are not fully understood but may reflect genetic traits and lifestyles. In addition, methodological differences between studies may also contribute to these differences.

1.1.2. Diagnostic methods

The acceptance criteria for diagnosing pneumococcal disease vary widely. Isolation of the pneumococcus from blood, pleural fluid or lung tissue cultures is regarded as definite pneumococcal disease.[79]

The detection of pneumococcal antigens in serum or urine by counter immuno-electrophoresis, latex agglutination or coagglutination[80,81] and the presence of antibodies to pneumolysin (a protein haemolysin common in all pneumococci) in serum, are considered as indications of possible pneumococcal infection.[82-84] However, these diagnostic methods are more likely to provide false positive and false negative results as compared with culture.[85-87]

The sensitivity for detecting the aetiology of pneumonia is 10% to 20% for blood culture,[88] 70% to 80% for CSF culture[88] and 80% to 100% for lung aspirate.[89,90] Thus, the proportion of pneumonias caused by pneumococci is greatly underestimated in studies that do not use lung aspirate. The absence of rapid, sensitive and specific tests is probably responsible for widespread use of antibiotics and may contribute to the emergence of drug resistance in pneumococci.

1.1.3. Risk factors

Certain factors are associated with an increased risk of and death from IPD (Table 1).[1,2] Although the risk of IPD is highest in young children, the elderly and adults with underlying chronic medical conditions are also at greater risk for IPD and they are more likely to die from the disease compared with young children in developed countries.[91]

Table 1. Risk factors for pneumococcal disease

Organism Virulence of colonising serotypes	**Age** <2 years, ≥ 65 years
Chronic medical disease Heart disease Pulmonary disease Liver disease Renal disease Diabetes Skull fracture (CSF leak)	**Immunocompromised conditions** HIV disease Haematological malignancy Non-haematological malignancy Asplenic dysfunction Sickle cell disease Immunoglobin deficiency
Life-style Drinking Smoking Drug use	**Socio-economic status** Low income Low education Poverty Over-crowding
Environment Day care attendance Residents in long-term care Winter Recent viral infections Exposure to tobacco smoke or smoke in outside kitchens Breast-feeding	

Studies have shown that the risk of disease increases in adults over 50 years of age and dramatically increases after 65 years of age.[92] US surveillance data have identified that although only one third of IPD cases are in the elderly, 65 years of age and above, over half of the deaths occur in this age group.[93] The reasons for the increased risk of pneumococcal disease in the elderly are not well defined but may relate to higher prevalence of chronic medical conditions[94] and poor antibody responses to polysaccharides.[95]

The increased risk of pneumococcal disease in infants and young children are due to defective anti-polysaccharide antibody synthesis and low complement activity.[96] The level of Immunoglobulin G2 (IgG2), which acts against bacterial capsules such as those of pneumococcus, meningococcus and *Haemophilus influenzae*, is lowest in children aged between 6 months and 24 months.[95] Thus, the risk of IPD is the highest during the first two years of life.[2]

Although pneumococcal pneumonia, bacteraemia and otitis media are more common in males than females,[97-103] the rate of NPC does not differ between sexes.[35] The reasons for this difference are not fully understood but may in part be due to higher prevalence of smoking, drinking and other risk factors in males.[99]

An increased incidence and mortality of IPD have been documented in patients with certain medical conditions.[94] Persons with chronic medical conditions have a 2- to 5-fold increased risk of developing disease[104] and a 2- fold risk of dying from it. The annual estimated incidence of IPD in persons with chronic lung conditions is 503 per 10^5 persons.[105] The incidence of IPD in different chronic medical conditions is scanty.

Splenectomised patients are at considerable risk of the disease, a 12.6-increase compared with the general population.[106] Additional data would be helpful in correct targeting of vaccine in persons with chronic medical conditions.

Immunocompromised persons due to disease (e.g. congenital immunodeficiency, human immunodeficiency virus (HIV) infection, leukaemia, lymphoma, multiple myeloma, Hodgkins disease, or generalised malignancy) or therapy (e.g. alkylating agents, antimetabolities, systematic corticosteroids, organ transplant) are at increased risk of IPD.[1,107] Studies have shown that the incidence of pneumococcal bacteraemia in cardiac transplant patients is extremely high, $3900/10^5$ patients in young children[108] and $3600/10^5$ patients in adults.[109]

The pneumococcus is the leading cause of bacterial pneumonia in HIV-infected persons.[110-113] The risk of disease increases with the progression of immunodeficiency.[114] HIV-infected persons have a 6-times higher risk of developing recurrent IPD than persons who are not HIV-infected.[115] Although the reason for the increased risk of disease in HIV patients is not clear,[116-118] high NPC and impaired mucosal immunity may predispose this group to disease.[119] The prevalence of carriage was two-fold higher in children with HIV than non-HIV infected children,[120] but no difference in carriage rate was detected in adults.[121]

Incidence rates of pneumococcal pneumonia or invasive disease in patients with acquired immunodeficiency syndrome (AIDS) are between 820 and $1,800/10^5$ patients in the US.[122-126] The risk of disease is reported to reduce with the use of highly active antiretroviral therapy (HAART) and co-trimoxazole and azithromycin prophylaxis in HIV-infected persons.[112,126-128] The US population based surveillance data showed that the incidence of IPD reduced dramatically from 1060 to $420/10^5$ persons, between 1994 and 1997, the time period for introduction of HAART.[129] No UK based data are available for this at-risk group.

It has been suggested that low socio-economic status, poor living conditions or high prevalence of chronic medical conditions are likely to be important risk factors for IPD in native populations[88,130] and in African Americans.[91] Studies have shown that the risk of disease remains higher in African Americans even after adjustment for multiple demographic, medical and socio-economic cofounders.[131-133] Limited data are available for the risk of disease associated with socio-economic status. Genetic risk factors for IPD such as sickle cell gene[134,135] may contribute to racial difference in disease incidence. However, genetic factors influencing the risk of disease are not fully defined and are difficult to separate from socio-economic factors.[105,133,136,137] Thus, the increased risk of disease in these groups appears to be due to multiple risk factors.

The occurrence of outbreaks or epidemics of pneumococcal disease has been well documented in chronic care facilities[3,138-142] namely a crowded, inadequately ventilated jail,[143] a homeless shelter,[144] hospital wards,[145,146] and a day care centre.[147] In nursing home settings, the pneumococcus is reported to be the most commonly acquired pneumonia.[148] The US data suggest that low vaccine coverage of less than 10% is a common factor for outbreaks of pneumococcal disease in elderly residents of long-term care facilities.[141] Studies have shown that day care centre attendance increases the risk for IPD in children.[149] The risk for IPD in children aged less than 2 years who attend day care centre was 36-fold higher in one Finnish study[150] and 2.3-fold higher in a US study,[151] compared with those who do not attend day care. Nevertheless, no significant difference was noted in those aged 2 years and above.[150]

The incidence of pneumococcal disease peaks during influenza and respiratory syncytial virus (RSV) epidemics,[152] with a marked increase in hospitalisation and mortality.[153-155] The frequency of IPD[7,103,156] and OM[51] peaks in midwinter. Studies have shown that pneumococcal NPC rates are highest in the autumn and winter among persons living in closed environments.[35,47] The exchange and acquisition of a new serotype increases dramatically during the winter and early spring,[157] which may explain the peak of disease in these periods. However, recent studies have failed to document an obvious seasonal trend in prevalence of carriage.[52,158]

Higher rates of pneumococcal carriage[121,159] and the incidence of IPD[105,133] have been detected in cigarette smokers.[105,133] US studies have estimated that smoking contributes to approximately half of IPD in healthy adults.[6,105] Although a decline in IPD has been observed with time, after stopping smoking, former smokers remain at high-risk for at least 10 years after stopping.[133] Thus, efforts to promote smoking cessation and targeting pneumococcal vaccination at those who continue to smoke could reduce the incidence of disease among smokers.

Numerous studies have found that alcoholism is the most common risk factor for pneumococcal bacteraemia in adults.[160,161] Incidence of IPD is reported to be higher in heavy alcohol users.[99,105] The available evidence shows that between 26% and 32% of adults with IPD are heavy alcohol users. The incidence of IPD is $62/10^5$ persons among heavy alcohol users.[105]

Studies in HIV-infected persons have shown that injecting drug users have an increased risk of pneumococcal pneumonia compared with those who are not injecting drug users.[121,126,162] A study in injecting drug users indicates the annual incidence of bacterial pneumonia to be 9.8% in persons with HIV-infection and 1.4% in those without HIV-infection.[163] Regardless of HIV status, however, an increased rate of pneumococcal disease has been reported among injecting drug users.[143]

Breast-feeding has been shown to protect against invasive *Haemophilus influenzae* type b (Hib) disease[164-167] but not IPD.[150] Although breast-feeding does not reduce the risk of OM in infants, it reduces the duration of middle ear effusion.[168] Studies have shown that protein in human milk inhibits the attachment of pneumococci and Hib in human oropharyngeal cells.[169,170] Since pneumococci colonise the nasopharynx primarily, the anti-adhesiveness of breast milk protein may not reach the nasopharynx. This may reduce the effectiveness of breast-milk against IPD.[150] Therefore, the role of breast-feeding in prevention of pneumococcal disease remains to be established.

A study in The Gambia found that the risk of pneumococcal disease was higher in infants from mothers who do not have a personal income.[171] The increased incidence of IPD in Afro-Americans may reflect racial differences in socio-economic status.[105,172] However, no difference in the incidence of IPD between races was observed in areas with similar income.[137]

Nearly 80% of paediatric IPD occurs in children less than 2 years of age.[107] The risk of IPD appears to be low in neonates with an estimated incidence between 4 and 7 per 10^5 live births.[77] Nearly 80% of paediatric IPD occurs in children less than 2 years of age.[107] The risk of IPD appears to be low in neonates with an estimated incidence between 4 and 7 per 10^5 live births.[77] Almost every child develops pneumococcal disease at least once before the age of 5 years, commonly with OM.[107] Furthermore, children with OM have a higher risk of IPD. It has been reported that children attending day care centres are at a greater risk of developing OM and thus have a higher risk of IPD.[58] The risk of pneumococcal disease may also be associated with exposure to cigarette smoking but the relationship has not been clearly demonstrated.

1.1.4. The burden of disease

Studies have shown that there is significant variation in the frequency of *S. pneumoniae* as a cause of community-acquired pneumonia (CAP) in different settings and locations (Table 2).[173] This may in part result from differences in diagnostic methods used in these studies. A meta-analysis of 122 reports of CAP between 1966 and 1995 found that the pneumococcus accounted for 73% of 6,000 cases with defined bacterial pathogens.[174] In the UK, pneumococcal disease is estimated to account for 22,000 hospital admissions and 3,000 deaths[175] each year.

Table 2. Proportion of cases of community-acquired pneumonia caused by pneumococcus

Country	Community		Hospital		Intensive care unit	
	Mean (%)	95%CI	Mean (%)	95%CI	Mean (%)	95%CI
UK	36.0	(29.9, 42.1)	39	(36.1, 41.8)	21.6	(15.9, 28.3)
Rest of Europe	8.4	(6.4, 10.8)	19.4	(18.4, 20.4)	21.8	(19.4, 24.2)
North America	-	-	11.3	(9.5, 13.0)	-	-
Australia & New Zealand	-	-	38.4	(33.9, 42.9)	-	-

1.1.4.1. Invasive pneumococcal disease

IPD is defined as a positive culture of the pneumococcus from a normally sterile site such as blood, CSF, or pleural space. More than 90% of IPD cases are bacteraemia. Of the rest, 5% to 10% are meningitis and less than 2% pericarditis, septic arthritis, osteomylelitis or peritonitis.[176] Bacteraemia is considered when patients have a positive blood cuture and no clinical focus. The reported incidence of IPD varies among surveillance reports

(Tables 3 & 4). This is likely to be due to factors related to case ascertainment rather than the true difference in incidence. These factors include variations in protocols for blood culture collection and processing in patients with febrile illness, the practice of antibiotic administration before blood culture, differences in surveillance systems and inherent differences in risk factors for the population under surveillance.[92,132,137]

Table 3. Incidence of invasive pneumococcal disease in infants and young children in selected countries

Country	Incidence rate per 10^5 persons/year	Age	Year	Reference
	All inavsive disease			
Sweden	15.3	< 5 y	1981-95	177
Germany	18.9	< 1y	1997-98	178
UK	33.2-48.1	< 1y	1995-99	77**,103,179
Denmark	39.4	< 1y	1981-99	180
Finland	45.3	< 2y	1985-89	181
Canada	55.3	< 5 y	1996	182***
Australia	71	< 2y	1992-2000	183
Chile	90.6	< 1y	1989-93	184
Australia	96.4	< 1 y	1997-99	185*
Israel	104	< 1y	1988-90	100
New Zealand	110	< 2y	1984-92	186
US	145-183	< 2y	1992-98	94*,187,188*
The Gambia	224-554	< 1y	1989-95	101 189
	Bacteraemia			
US (South California)	143	< 2 y	1992-95	187
US (South Carolina)	162	< 2 y	1986-87	172
US (New York)	175.5	< 1 y	1985-89	190
Finland	24.2	< 5 y	1985-89	181
Sweden	13.8	< 1y	1970-80	99
Switzerland	3.6	< 2 y	1985-94	191
UK	19.4-35	< 1 y	1993-95	7,77**
	Meningitis			
Finland	4.7	< 2y	1985-89	181
Switzerland	5.6	< 2y	1985-94	191
US	6.6-10	< 2y	1992-95	187,188*
UK	9.4-15.7	< 1y	1993-99	7,77**,179
Germany	9.7	< 1y	1997-98	178
Israel	11.1	< 2y	1988-90	100
Sweden	12	< 1y	1970-80	99
Australia	17	< 2y	1992-2000	183
Denmark	17.4	< 1y	1981-99	180
New Zealand	23	< 2y	1984-92	186
Chile	26.7	< 1y	1989-93	184
The Gambia	34	< 1y	1993-95	189

Niger	149.6	< 1y	1981-96	192

*y = year(s), * Active surveillance, ** Enhanced surveillance, *** Sentinel surveillance, The remainder were based on passive surveillance or did not indicate the type of surveillance*

Table 4. Incidence of invasive pneumococcal disease in the elderly in selected countries

Country	Incidence rate per 10^5 persons/year	Age	Year	Reference
	All invasive disease			
France	17.8	≥65 y	1994-98	193
Sweden	20.4-37	≥65 y	1981-95	177
UK	21.2-44.7	≥65 y	1995-99	77**, 103
Australia	25-100	≥65 y	1997-99	185*
Finland	27.1	≥65 y	1985-89	181
Israel	55	≥65 y	1994-96	102
US	55.9-59.7	≥60 y	1995-98	94*, 188*
	Bacteraemia			
Sweden	10.4	≥65 y	1970-80	99
UK	23.6	≥65 y	1993-95	7
US (South California)	31	≥65 y	1992-95	187
Canada	46	≥65y	1996	182***
US (South Carolina)	52.8	≥65y	1986-87	172
US (New York)	56.3	≥65 y	1985-89	190
UK	78	>80 y	1993-95	194
US (Dallas)	80	≥65 y	1995	105*
	Meningitis			
UK	0.85-1.2	≥65 y	1995-99	77**
US (South California)	<1	≥65 y	1992-95	187
Sweden	1.2-3.7	≥60 y	1970-95	99, 177
US	1.9	≥60 y	1995	188*

*y = year(s), * Active surveillance, ** Enhanced surveillance, *** Sentinel surveillance, The remainder were based on passive surveillance or did not indicate the type of surveillance*

The overall annual incidence of IPD for all ages is 6.6 to $10.3/10^5$ population in the UK.[7,77,103] The incidence of IPD is greatest in young children, the elderly and persons with certain underlying medical conditions.[1] The estimated incidence of IPD is 33.2 to $48.1/10^5$ infants aged less than one year in the UK,[77,103] which is much lower than cited for the US, 140 to $167/10^5$ in children aged less than two years[6,94,105,172,187,195] In those aged 65 years and above, reported rates of IPD per 10^5 persons range from 25 to 90 cases in Europe and North America.[92] Several US studies have highlighted a higher rate of IPD for African Americans than white Americans.[94,132,188] The highest reported rates of IPD are in The Gambia and native populations in the US, New Zealand, and Australia (Table 5). The estimated case-fatality rate for bacteraemic pneumococcal disease is 4.5% in children,[196] 20% in young adults, 30% to 55% in the elderly[74,197] and 76% in those who required Intensive Care Unit support.[198] Although there are wide geographical variations in rates for IPD, the incidence of pneumococcal meningitis is comparable in Europe and North America. This suggests that the observed differences in IPD may be largely due to variations in blood culture sampling.

Table 5. Incidence of invasive pneumococcal disease in native populations

Native	Incidence rate per 10^5 persons/year	Reference §
	All invasive disease	
Young children		
Aboriginal **	297-326	183
Aboriginal **	754	199
Aboriginal ***	935	200
Navajo*	664	201
Alaska **	624	202
Alaska **	1235	203
Apache **	1820	204
Elderly		
[2]Aboriginal	121	200
[2]Aboriginal	114	199
[2]Alaska	145	203
[1]Alaska	186	202
[2]Apache	172	204

** Children aged less than 1 year, ** Children aged less than 2 years, *** Children aged less than 5 years*

[1] Elderly aged 65 years and above, [2] Elderly aged 60 years and above

§ *Based on passive surveillance or did not indicate the type of surveillance*

In the UK, the pneumococcus became the second most common cause of bacterial meningitis in young children after the implementation of Hib conjugate vaccine into the primary immunisation programme in 1992.[205] The pneumococcus is the most common aetiological agent of bacterial meningitis in adults[206] and the elderly.[188,207] The overall annual incidence of pneumococcal meningitis for all ages is estimated to be 0.4 to $0.8/10^5$ population, with the highest incidence of 9 to $15/10^5$ in infants aged less than one year in the UK.[7,77] Case-fatality rates range from 7% to 30% in children aged less than 5 years and reaches 50% in the elderly.[207-210] Of those who survive, 25% have neurological sequelae and 32% have hearing loss.[210] A recent UK study in 1717 children aged 5 years or under with bacterial meningitis found that the risk of disability was higher in children with pneumococcal meningitis than *H. influenzae* or meningococcal meningitis.[211] In addition, the rapidly spreading antimicrobial resistance has an important impact on pneumococcal meningitis, making antibiotic treatment more difficult and costly.

1.1.4.2. Non-invasive pneumococcal disease

Non-invasive pneumococcal disease (NIPD) includes pneumonia, otitis media, sinusitis and other upper and lower respiratory infections when the pneumococcus is recovered from sputum, nasopharynx and other superficial sites. It is considered to be more difficult to diagnose NIPD due to the empirical and widespread use of antibiotics, relatively common nasopharygeal colonisation and the need for tympanocentesis. As a result, an accurate figure for the incidence of NIPD in the UK remains unknown.

Nevertheless, the pneumococcus is considered to be the most common cause of upper and lower respiratory infections and OM in the UK.[212] An estimated incidence of pneumococcal pneumonia per 100,000 persons is 100 in all ages,[212] 500 in children aged less than five years[213] and 200 to 400 in the elderly.[173,214]

OM is one of the most common diseases of childhood and is caused by three key pathogens: the pneumococcus, *Haemophilus influenzae* and *Moraxella catarrhalis*.[215,216] Data from 13 published studies on bacteriology of OM in 4157 children show that the pneumococcus accounts for 20% to 37% of cases, followed by *H. influenzae* (20%), *Moraxella catarrhalis* (6%), *Streptococcus pyogenes* (2%), *Staphylococcus aureus* (2%) and others (6%).[217] Similar pathogens were responsible for acute OM in adults.[218] An international study, conducted in Eastern and Central Europe, Israel and the US, showed that the pneumococcus is the most frequent cause of OM pathogen in Europe.[216] The distribution of causative pathogens in bacterial sinusitis is comparable to those in OM.[219]

Acute OM occurs in 7 out of every 10 children.[217] Of these, repeated episodes develop in 30% and chronic OM with effusion in 5% to 10% of cases. Recurrent OM can affect hearing, language acquisition and achievement in school[220,221] in 20% of cases.[222] The peak incidence of OM occurs at six to 18 months of age.[215,223,224] The annual estimate for episodes of pneumococcal OM for children aged less than two years in the UK is between 180,000 and 540,000.

Acute OM is the most common reason for antibiotic prescription in Europe and the US.[225-227] In the UK, 97% of children with OM receive an antibiotic prescription when they see their general practitioners (GPs).[225] The widespread use of antibiotics for acute OM is associated with an increase in rates of drug resistant bacterial pathogens.[228,229] Children with frequent OM episodes are more likely to carry multi-drug resistant pneumococci.[230]

1.1.5. Antibiotic resistant pneumococci

Pneumococcal resistance to a particular antimicrobial agent is variable and is measured by the minimum inhibitory concentrations (MIC). Isolates with MICs for penicillin < 0.06 μg/ml, between 0.12 to 1.0 μg/ml and ≥ 2 μg/ml are considered sensitive, intermediately resistant and high-level resistant respectively.[231] Multidrug resistance is defined as resistance to three or more antimicrobial agents.[232,233]

The prevalence of pneumococcal resistance to penicillin and other antibiotics is increasing in the UK and other countries.[234] In England and Wales, the proportion of penicillin resistant (PR) pneumococcal isolates has increased from 1.5% in 1990 to 3.9% in 1995[235] and to 3.6-7.4% in 1997/1998.[236] The proportion of erythromycin resistance has also increased, from 2.8% in 1990 to 8.6% in 1995[235] and to 11% in 1997/1998.[236] The prevalence of resistance to penicillin and erythromycin was low in Scotland but an increase of 1.5% to 2.3% and 1.4% to 4.5%, respectively, was documented between 1992 and 1995.[70] Geographic variations in prevalence of antibiotic resistant pneumococci have been observed both between and within countries (Table 6).[237-239] The highest resistance has been reported in some parts of Europe[240,241] Asia[242] and the US.[243] In Europe, much higher rates of PR pneumococci have been detected in Hungary,[240] Spain,[241] France[244] and Portugal.[245]

Although rates of PR pneumococci are highest in young children,[149] data from the US indicate an increased rate of penicillin resistance in pneumococci in the elderly.[246,247] In some parts of the US up to 40% of invasive isolates have shown reduced susceptibility to penicillin in the elderly.[247] An outbreak[140] and a cluster of (multi) antibiotic resistant pneumococcal disease[248] have been reported among institutionalised elderly with low vaccine coverage in the US, suggesting the need for pneumococcal polysaccharide vaccination in residents of nursing facilities. Specific data on the prevalence of antibiotic resistant pneumococci in the elderly and persons in long-term care facilities in the UK have not yet been reported.

Table 6. Penicillin non-susceptibility in pneumococci in selected countries by continent

Region	Year	Resistance %	Reference
Europe			
UK	1990-1998	<1 - 7.4	236
UK	1995	2.9	7
UK	1995-99	4.6	77
Germany	1998	6.7	244,249
Poland	1997	14.4	250
Iceland	1998	32.8	244
Hungary	1997	43	251
France	1998	53.3	244
Spain	1999	60.1	252
North America			
Canada	1997-98	21.2	253
US	1997	49.7	254
Canada	1994	54.9	255
Latin America & Caribbean			
Colombia	1994-96	15.6	256
Seven countries*	1997	23.6	257
Six countries**	1993-99	28.6 (20.7-33)	258
Oceania			
New Zealand	1997	17	259
Australia	1997	25.4	260
Asia			
India	1996-97	3.8	242
China	1996-97	9.8	242
Bangladesh	1993-97	12.7	261
Japan	1998	30.9	244
Thailand	1992-94	37.2	262
Hong Kong	1999-2000	58	263
Singapore	1997-99	63.3	264
Vietnam	1996-97	60.8	242
Taiwan	1998-99	76	265
Korea	1996-97	79.7	242

Africa			
Kenya	1992-96	22.6	266
South Africa	1998	43.8	244

** Argentina, Brazil, Chile, Mexico, Panama, Venezuela, and West Indies*
*** Mexico, Brazil, Argentina, Chile, Colombia, Uruguay*
Non-susceptible included intermediate and resistant isolates (MIC level $\geq$ 1.02 μg/ml)

Worldwide data indicate six serotypes (6B, 9V, 14, 19A, 19F and 23F) to be the most frequent causes of antibiotic resistant pneumococcal disease.[267] These serotypes are also mostly associated with multidrug resistance,[268] particularly, serotypes 6B and 23F.[195,269] NPC with these strains is common in children,[33,267] suggesting that young children may play a major role in the spread of resistant pneumococcal strains in the community.[270]

The molecular epidemiology of penicillin resistant pneumococci in 15 countries found that serotypes 23F and 9V clones are responsible for the global spread of antibiotic resistant pneumococcal isolates.[271] The most prevalent penicillin resistant serotypes are 23, 6 and 9 in the UK.[272-275] Several studies have reported that serotypes 6B, 9V, 14, 19A (19F), and 23F are the most frequent cause of outbreaks of antibiotic resistant pneumococcal disease in paediatric hospitals[276,277] day care centres[147,230,278,279] and nursing homes.[140] All these serotypes associated with antibiotic resistance are included in the formulations of PPV and PCV.

A relationship between antibiotic use and an increase in rates of antibiotic resistant pneumococci has been demonstrated in some parts of Europe,[226,280-284] Canada,[285,286] the US[140,226,268,287,288] and Australia,[289] but not in Scotland. US studies have documented an association between antibiotic resistant pneumococci and socio-economic or racial status.[137,195,290] Although the incidence of invasive disease is at least 3-fold higher in African Americans than White Americans, the latter are at greater risk for antibiotic resistant pneumococcal disease, suggesting greater use of antimicrobial agents, perhaps through increased access to health care.[137,291,195] Other major risk factors for carriage or infection with penicillin non-susceptible pneumococci are young age, day care centre attendance, otitis-prone conditions and prior hospitalisation.[149]

The emergence of antibiotic resistance is likely to have an impact on the choice of treatment regimen.[210] Pneumococci with high-level resistance to penicillin and other antibiotics would have serious implications for patients with invasive disease, particularly meningitis.[11,292] Treatment failures and fatal outcomes in patients with meningitis caused by beta-lactam resistant pneumococci have been documented.[293-296] Although it has not been consistently documented in the US studies,[297,298] there is also strong evidence that penicillin resistant pneumococcal strains are associated with increased adverse medical outcomes[6,8,299,300] such as high mortality (MIC$\geq$ 2.0 mg/ml)[8] and longer hospitalisation (3.7 days) (MIC$\geq$ 1mg/ml)[6] than patients with penicillin susceptible pneumococcal disease.

Key strategies to control the spread of antibiotic resistant pneumococci include improved antibiotic resistance surveillance, the promotion of judicious antibiotic use and improved use of pneumococcal vaccine.[149,288,301] Interventions targeting patients and health care providers are also an essential part of reducing unnecessary use of antimicrobial agents.[288] Accurate population-based data on the overall prevalence and the distribution of serotypes associated with antimicrobial resistance in pneumococci are necessary in order to implement effective public health measures in Scotland.

1.1.6. Economic impact of pneumococcal disease

The total health care cost of pneumococcal disease has not been determined in the UK. However, the annual cost of treating CAP is estimated at £440 million (1992/93 prices).[302] The available data show that respiratory infections are the most common reason for general practice medical consultations, accounting for about 30 million antibiotic prescriptions and over 3 million sickness prescriptions annually in the UK.[212] The average cost is £389 for myringotomy and £303 for grommet insertion, which results in nearly £30 million per year for surgical treatment of glue ear in England and Wales.[303] At present, data are lacking on the economic impact of pneumococcal disease in the UK and studies on economic evaluation in this area are required. These data are an essential component of calculating the cost-effectiveness of introducing pneumococcal vaccines and prioritising treatments and preventive measures in order to manage the escalating costs of health care.

1.2. Prevention of pneumococcal disease

1.2.1. Immunity against the pneumococcus

1.2.1.1. Natural immunity

Defence against pneumococcal disease includes the activity of type-specific antibodies, opsonisation and efficient phagocytosis and killing by neutrophils.[29] The development of antibodies against the polysaccharide capsule occurs following pneumococcal disease or exposure to pneumococci.[304-307] Serotype-specific antibodies directed to capsular polysaccharides are protective against pneumococcal disease.[308] The development of natural immunity[309] appears to relate to the induction of mucosal IgA with NPC[310] and serum IgG to pneumococcal surface protein A (Psa A), pneumococcal surface adhesin A (Psa A) and pneumolysin.[311] The immune response to pneumococcal polysaccharides is influenced by genetic factors.[312,313] However, the molecular basis of the natural immune response to pneumococci is poorly understood.

1.2.1.2. Vaccine induced immunity

Vaccines based on pneumococcal capsular polysaccharides induce serotype-specific antibodies.[308,314-316] Currently, the exact antibody level that is "protective" is unknown. However, certain levels of antibody after vaccination or infection are considered to be associated with protection.[317] The level of 0.15 $\mu g\ ml^{-1}$ and 1.0 $\mu g\ ml^{-1}$ are considered as surrogates for short-term and long-term protection respectively.[318] It is generally assumed that vaccines containing serotypes 6B and 19F induce cross-reactive antibodies to serotypes 6A and 19A.[319] However, studies have shown that vaccine serotypes 6B and 19F do not always provide functional antibody to cross-reactive serotypes 6A and 19A.[320-322] Current clinical trials of pneumococcal vaccines should determine the presence of the cross-reactive protection within vaccine serotypes.

1.2.1.2.1. Pneumococcal polysaccharide vaccines

A 14-valent PPV containing serotypes 1, 2, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18C, 19F, 23F and 25[319] was replaced with a 23-valent PPV in 1989 in the UK,[15] the latter including additional serotypes, 5, 6B, 9V, 10A, 11A, 15B, 17F, 19A and 33F.[323] Overall, the current vaccine covers between 88% and 90% of IPD causing serotypes in adults and 85% in older children in the UK, other parts of Europe and North America.[76,77,319,323,324] The evidence indicates that the level of PPV-induced antibodies is lower in patients with chronic obstructive pulmonary disease,[325] immunocompromised conditions,[326,327] the elderly[328-330] and young children[331] compared with healthy adults.

There are two major study designs that have been used to evaluate the efficacy and effectiveness of pneumococcal vaccines. These include experimental studies (randomised controlled trials, RCT) and observational studies (cohort, case-control and indirect cohort studies).[332] Although RCTs are regarded as the most rigorous method of assessing vaccine efficacy, they are sometimes impractical due to ethical, financial and logistical factors.[12,332,333] In addition, lack of sufficiently sensitive and specific diagnostic methods and the relatively low incidence of IPD represent major obstacles in determining efficacy of PPV.[334]

In contrast, case-control and indirect cohort studies have advantages in rapid gathering of data and higher statistical power to evaluate vaccine effectiveness[332] and in certain circumstances are a more pragmatic approach for evaluating the impact of vaccine under normal clinical practice.[335] Nevertheless, these studies are more likely to be associated with bias.[336] Both case-control and indirect studies require positive pneumococcal isolates from a sterile body site, accurate records of vaccination status and a study population with vaccine coverage of at least 15%. In the past, the US was the only country where vaccine coverage was adequate to permit the use of these research designs. However, surveys in Europe show that coverage of PPV is 15% in the UK[14] and 20% in Belgium[337] in 1998. Thus, these methodologies could be used in some Western European countries to confirm the earlier results of US studies.

There are five systematic reviews or meta-analyses of RCTs, which evaluate PPV effectiveness (Table 7).[338-342] Unfortunately, these papers have reached differing conclusions highlighting problems with meta-analysis, which have been subject to debate in the journals.[343] Although the methodology used in these reviews differs, no studies assess vaccine efficacy by the type of vaccine and its outcome measures and patient population. None of these studies have clearly concluded that PPV is effective against non-bacteraemic pneumonia in industrialised populations. It was not surprising that Moore et al[341] failed to show the efficacy of the vaccine, since they did not include three large RCTs, which concluded the vaccine was protective. The recent systematic review[339] concluded that PPV has protective effects for mortality and all causes of pneumonia in non-industrial populations. These clinical outcomes were not demonstrated in industrialised populations with the exception of pneumococcal bacteraemia. However, a reduction in bacteraemia did not show any statistical significance. As the authors stated, the small sample size in most of the trials carried out in industrialised countries is likely to be the major reason for not demonstrating a clear benefit of vaccine in older patients.

The other three meta-analyses[338,340,342] included RCTs found that the vaccine was effective in preventing invasive pneumococcal disease caused by vaccine serotypes in immunocompetent adults. However, two of these studies[338,342] representing 40,431-48,837 patients, found lack of benefits in older patients or persons with high-risk conditions (e.g. immunosuppression or chronic organ dysfunction). In contrast, the Canadian study[340] consisting of more than 65,000 patients suggests no evidence of lower effectiveness of vaccine in the elderly, institutionalised patients or persons with chronic disease for systematic pneumococcal disease due to all pneumococci. Thus, it appears that the sample size is critical in demonstrating the protective benefits of PPV in specific target groups as in individual clinical trials.

However, the Canadian study did not find statistically significant benefit for any outcome measure in patients with chronic organ dysfunction and the elderly, if the open randomised trial published in 1947 was removed from the analysis. The conclusion from these meta-analyses suggest that PPV may not offer any benefits for the elderly and patients with immunocompromised conditions but the validity of the meta-analyses which gathered the results of studies with different outcome measures, inadequate samples or limitations in methodology has been highlighted.[344]

Table 7. Conclusions of four systematic reviews or meta-analysis of pneumococcal polysaccharide vaccine efficacy

Reference	Type of review	Conclusion
Fine MJ, *et al*[338]	Meta-analysis of 9 trials published up to 1991	Pneumococcal vaccination appears efficacious in reducing bacteraemic pneumococcal pneumonia in low-risk adults. However, evidence from RCTs fails to demonstrate vaccine efficacy for pneumococcal infection-related or other medical outcomes in the heterogeneous group of subjects currently labelled as high risk.
Hutchison BG, *et al*[340]	Meta-analysis of 13 trials published up to November 1996	Vaccination with PPV can be expected to reduce the risk of systemic infection due to pneumococcal types included in the vaccine by 83% and systemic infection due to all pneumococci by 73%. No evidence was found that the vaccine was less efficacious for the elderly, institutionalised people, or those with chronic disease.
Moore RA, *et al*[341]	Systematic review of 9 trials published up to 1999	The weight of evidence is that PPVs have yet to be shown to work in the types of people given them in industrialised countries. The only real evidence that they do comes from two improperly randomised studies from the 1940s.
Watson L, *et al*[339]	Systematic review and meta-analysis of 16 trials published up to March 1999	For studies carried out in the West, there was no protective effect found on mortality, all pneumonia or pneumococcal pneumonia, although there was a protective trend for pneumococcal bacteraemia, a surrogate outcome. In third world studies a significant protective effect was found for the three clinical outcomes.
Cornu, *et al*[342]	Meta-analysis of 14 trials published between 1966 and 1999	Vaccination is effective in preventing 71% definite pneumococcal pneumonia, 40% presumptive pneumococcal pneumonia and 32% mortality due to pneumonia in immunocompetent adults. No protection is observed for all-cause pneumonia or death. Vaccine efficacy is not apparent for the elderly, $\geq$55 years of age, mainly due to low statistical power.

PPV has been shown to be between 76% and 92% efficacious against pneumococcal pneumonia and pneumococcal bacteraemia in RCTs conducted in military recruits,[345] South African gold miners[346,347] and adults in Papua New Guinea (Table 8).[348]

However, the results of 7 RCTs[136,349,350-355] and two prospective intervention studies in which PPV was administered with or without influenza vaccine[353,356] in the elderly population are contradictory (Table 8). Indeed, surprisingly, an increased number of pneumococcal disease events was even observed for vaccine recipients among HIV-1 infected adults in Uganda.[355] Differences in study populations and methods such as whether a placebo was used and the choice of placebo, make these results difficult to compare.[334] In contrast to the results from Finland and Sweden, the additive health and economic benefits of pneumococcal and influenza vaccination have been demonstrated in the elderly with chronic lung disease in the US.[357] One prospective study in Canada also showed that pneumonia and other respiratory infections were more likely to occur in unvaccinated elderly residents in long-term care facilities.[358] Differences in individuals responses to polysaccharide vaccine and against pneumococci suggesting that the effectiveness of PPV is likely to be varied among patients with different at-risk conditions.[359] However, very few clinical trials have assessed the efficacy of PPV vaccine by separating subgroups of patients. A small randomised trial, which assessed the immunogenicity of 14- to 17-valent PPV in patients with chronic obstrtuctive pulmonary disease (COPD) or bronchogenic carcinoma observed that PPV was immunogenic in these patients[325,360,361] but a rapid decline of antibody after vaccination was noted in one study.[325]

Five case-control and four indirect cohort studies have been conducted to assess the effectiveness of PPV in high-risk groups (Table 9). With the exception of one study,[362] PPV was estimated to be 48% to 81% effective against IPD in immunocompetent elderly persons and persons with underlying medical conditions. However, protection was lower in those with sickle cell disease, haematological malignancies[363] and recurrent otitis media.[364] The one study, which failed to demonstrate vaccine effectiveness, is thought to be due to incomplete ascertainment of vaccination status of the study subjects and possible bias in the selection of controls.[365,366]

Early data from RCTs in Papua New Guinea showed that PPV was 50% efficacious in reducing death from acute lower respiratory tract infections in children aged between four months and two years.[367,368] No effectiveness was noted for respiratory and otitic complaints in studies in Australia.[369,370] PPV has been shown to reduce the incidence of OM caused by vaccine serotypes associated with good antibody responses in young children in the US[371,372] and Finland[364] but not in other US studies.[373] Although one US study noted a 50% decrease in the incidence of subsequent ear infections in African Caribbean American children aged between 6 and 11 months, there was no reduction in White American children.[374] A recent US retrospective study in children aged two to five years found that the vaccine effectiveness was 63% for all children and 62% for children with sickle cell disease.[375] Studies that failed to show evidence of the benefits of vaccination in young children are probably due to poor humoral response in this age group. Conflicting results may also relate to genetic factors, differences in measurement of antibodies and age of study population and the prevalence of non-vaccine serotypes or adult serotypes.

Based on these data, the evidence of PPV is restricted to the prevention of IPD in immunocompetent older children and adults and the elderly, many of whom have high-risk conditions.[376] Its effectiveness in high-risk patients against pneumonia (in the absence of bacteraemia) is not certain. At present, insufficient data are available to support the effectiveness of PPV in preventing non-bacteraemic pneumonia in the elderly and otitis media and other non-invasive pneumococcal disease in young children.

Table 8. Summary of randomised controlled trials and prospective cohort studies of pneumococcal polysaccharide vaccine efficacy in high-risk groups

Reference	Trial site	Trial type	Characteristics of subject	Outcome measure	Vaccine type	% Efficacy (95%CI)	No of subjects
Macleod et al 1945[345]	US	Single blind	Military recruits	Pneumonia	4-valent	85 (79,100)	17035
Kaufman et al 1947[349]	US	Single blind	Institutionalised elderly	Pneumonia Bacteraemia	4-valent 4-valent	92 (72,98) 93 (45,100)	11,000
Austrian et al 1976[377]	South Africa	Single blind	Gold miners	Pneumonia Bacteraemia	13-valent 13-valent	79 (65,88) 82 (66,92)	2973
Smit et al 1977[347]	South Africa	Double blind	Gold miners	Pneumonia Pneumonia	6-valent 12-valent	76 (52,89) 92 (49,100)	3019
Riley et al 1977[348]	Papua New Guinea	Double blind	Persons >10 years	Bacteraemia	14-valent	86 (<0, 99)	11958
Austrian et al 1981 Unpublished	US	Single blind	Mentally ill elderly	Pneumonia	12-valent	15 (<0,52)	1300
Gaillat et al 1985[350]	France	Open	Nursing home residents	Pneumococcal pneumonia	14-valent	77 (51,89)	1686
Simberkoff et al 1986[351]	US	Double blind	Elderly	Pneumonia Bronchitis	14-valent 14-valent	<0 (<0,45)	2295
Koivula et al 1997[354]	Finland	Double blind	Elderly	Pneumococcal pneumonia	14-valent	59 (6, 82)	2837
Ortqvist et al 1998[352]	Sweden	Double blind	Elderly	Pneumonia Pneumococcal pneumonia	23-valent 23-valent	-28 (-150,34)	691
French et al 2000[355]	Uganda	Double blind	HIV-1-infected adults ($\geq$ 15 years)	Pneumococcal bacteraemia Serotype specific pneumococcal bacteraemia All pneumococcal disease All pneumonia Death	23-valent	-47 (34, -227) -110 (14, -416) -40 (29, -178) -89 (-12, -221) 1 (20, -21)	1392

Prospective cohort study							
*Honkanen et al 1999[353]	Finland	Cohort	Population based study (included healthy elderly and elderly with chronic medical disease)	Pneumonia Pneumococcal pneumonia Pneumococcal bacteraemia	23-valent	-20 (-50, 10) -20 (-90, 20) 60 (-40, 90)	43,500
*Christenson et al 2001[356]	Sweden	Cohort	Population based study	Influenza Pneumonia Pneumococcal pneumonia Invasive Pneumococcal disease Death	23-valent	-46 (34, 56) -29 (24, 34) -36 (3, 58) -52 (1, 77) 57 (55, 60) 57 (55, 60)	100,242
Loeb et al 1999[358]	Canada	Cohort	5 nursing homes	Pneumonia Other lower respiratory infections	-	Likely to be protective	229/104

** Received both influenza and pneumococcal polysaccharide vaccines*

Table 9. Summary of case-control and indirect cohort studies of pneumococcal polysaccharide vaccine effectiveness in high-risk groups

Reference	Outcome measure	% Effectiveness (95%CI)	Location	No of subjects
[2]Broome et al 1980[378]	Invasive infection	36*all ages (≥2 years) 60**(>10 years old) <0***	US CDC (isolates from 46 hospitals in 26 States)	427/427
[1]Shapiro et al 1984[379]	Invasive infection	67**(13,87) (≥18 years) <0%***	New Haven, US	90/90
[2]Bolan et al 1986[380]	Invasive infection	61*(1,85) (≥2years) 64**(47,76)	CDC, US (isolates from 37 hospitals in 22 States)	1887/1887
[1,2]Forrester et al 1987[362]	Bacteraemia	<0* (<0,35) elderly	Denver, US	89/89
[1]Sims et al 1988[381]	Invasive infection	70** (37,86) elderly	Philadelphia, US	122/244
[1,2]Shapiro et al 1991[382]	Invasive infection	56 (42, 75)* (≥18 years) 61 (47, 72)** 21 (<0, 60)*** 71 (30,88) elderly	Connecticut, US	983/983
[2]Butler et al 1993[363]	Invasive infection	57 (45,66)* (≥5 years) 49 (23,65)** 49 (22,64)*** 75(57,85) elderly	CDC, US (isolates from 54 hospitals in 26 States)	2837/2837
[1]Farr et al 1995[336]	Bacteraemia	81 (34,94)* (≥2 years)	Charlottesville, US	85/152
[1,2]Davidson et al 1995[383]	Invasive infection	79 (49,92)** adults 64 (32,81)	Alaska, US	87/87[1] 159/159[2]
[2]Fiore et al (1999)[375]	Invasive infection	63 (8,85) All children 62 (-294,98) Children with SCD 84 (40,96) Children without SCD 93 (45,100) ****All children	CDC, US (isolates collected through hospital laboratory-based surveillance)	145/173 39/46 106/127 19/47

[1] case control study, [2] indirect cohort study, CDC = Centre for Disease Control and Prevention, SCD = sickle-cell disease

**All conditions*

***With underlying medical conditions (chronic lung, heart, liver, renal, diabetes mellitus and alcoholism)*

**** Immunocompromised conditions (splenic disorders, sickle cell disease, haematological malignancies, organ transplant and systematic lupus erythematosus)*

***** Effectiveness for the serotypes not included in the 7-valent conjugate vaccine*

Current evidence suggests that PPV is safe and does not cause serious adverse events.[338,384] A review of 1099 elderly receiving two doses of PPV found that revaccination does not cause adverse events requiring hospitalisation.[385] There are no reports to date of severe febrile reactions or anaphylactic reactions after initial vaccination or revaccination.[376] Simultaneous administration of influenza and pneumococcal vaccines has been shown to produce a satisfactory antibody response without increased adverse reactions.[386] The incidence and severity of adverse reactions after more than two doses of PPV are not known.

PPV is poorly immunogenic in children aged less than two years,[387] the age group with the highest incidence of invasive and mucosal infection. As a consequence, it is not recommended for them. Since polysaccharide antigens are T-cell independent, the vaccine is unable to induce immunological memory and does not reduce carriage.[316] An immune response of capsular polysaccharide is relatively short-lived in older adults and persons with underlying diseases.[388,389] In addition, it does not protect against non-invasive disease such as pneumonia or otitis media.[1] Thus, conjugate vaccines have been developed in response to these problems. Linking polysaccharides to protein carriers converts the polysaccharide from T-cell-independent antigens to T-cell-dependent antigens.[390] This results in induction of immunological memory, maturation of immune response in infants, the elderly and those with immunocompromised conditions.[4,391] Conjugate vaccines have proven highly successsful in reducing invasive *H. influenzae* type b[392] and group C meningococcal disease.[393]

1.2.1.2.2. Pneumococcal conjugate vaccines

Current PCV formulations include the 7 to 11 serotypes causing the majority of pneumococcal disease in children (Table 10).[72,316] All PCV formulations also include serotypes 6, 14, 19 and 23, which in polysaccharide vaccines are less immunogenic in children[331,394] and strains currently resistant to antimicrobial agents worldwide.[267] The 7-, 9- and 11-valent conjugate vaccine serotypes cover 75%, 80% and 87% of IPD respectively in children less than 5 years of age in the UK.[77] The coverage of IPD with these vaccines decreases in older children and the elderly in the UK and US.[77,363] The serotypes in the 9- and 11-valent conjugate vaccine are responsible for 76-93% of IPD in Europe and the US.[376] Coverage of non-invasive pneumococcal isolates in young children was 65% in the US with 7-valent conjugate vaccine.[68] Data on coverage of conjugate vaccines for non-invasive disease have not yet been reported in the UK. Serotypes included in the 9-valent and 11-valent conjugate vaccines covered over 60% of all pneumococcal isolates worldwide (except CSF isolates in Asia where coverage of both vaccines was only 40% and above) from pneumonia patients, both young children and adults.[78]

PCVs are safe and immunogenic in infants,[20] the elderly and persons with immunocompromised disorders (HIV, Hodgkin's and sickle cell diseases),[395,396-398] recurrent respiratory infections,[399,400] native American Indian[401] African and Asian descents.[316,402-407]

Table 10. Candidate pneumococcal conjugate vaccines in clinical trials

Vaccine serotypes	Carrier proteins	Manufacture	Clinical studies
7-valent (4, 6B, 9V, 14, 18C, 19F, 23F)	CRM_{197} protein	Wyeth Lederle vaccine	Completed Licensure obtained in the US * and Europe
7-valent (4, 6B, 9V, 14, 18C, 19F, 23F)	Meningococcal OMP	Merck Research Laboratories	Phase II/III
8-valent (3 with 7-valent vaccine serotypes)	Diphtheria toxoid	Pasteur Merieux Connaught	Phase I/II
8-valent (3 with 7-valent vaccine serotypes)	Tetanus toxoid	Pasteur Merieux Connaught	Phase I/II
9-valent (1, 5 with 7-valent vaccine serotypes)	CRM_{197} mutant diphtheria protein	Wyeth Lederle vaccine	Phase III
11-valent (1, 5, 3, 7F with 7-valent vaccine serotypes)	Diphtheria toxoid or tetanus toxoid	Pasteur Merieux Connaught	Phase I/II

* *Included in the routine childhood immunisation programme*

Antibody responses to PCVs vary according to serotype and vaccine formulation.[408] Studies in developed and developing countries have reported that PCVs are immunogenic in infants aged six to eight weeks.[316,409] After three doses with PCVs, anticapsular antibody levels are raised 3.5 to 20 fold compared with pre-immunisation levels.[410-413] The level of antibody at seven months of age after a series of three doses ranges from 0.5 to 4.29 μg/ml for poorly immunogenic serotypes and to 1.13 to 14.09 μg/ml for the most immunogenic serotypes.[316] Serotypes 6B, 18C and 23F are less immunogenic than serotypes 4, 9V, 14 and 19F[414] and require a second dose of vaccine to elicit protective antibody levels.[415,416] The correlation between vaccine-induced efficacy and anticapsular antibody as measured by radio immuno-assay (RIA), enzyme-linked immunosorbent assay (ELISA) and functional assay (opsonophagocytic) has not been evaluated.

At present, there are limited data on PCVs in adults and the elderly. Of the eight studies of PCVs in adults and the elderly,[417] six studies showed that PCVs elicited higher antibody responses than PPV in younger adults.[391,396,418-421] In contrast, two other studies in persons aged 50 years above did not show significant advantages in antibody responses over polysaccharide with the conjugate vaccines.[391,421] Although there is no clear explanation, low baseline immunity to diphtheria protein (prevaccination anti-diphtheria antibody level <0.55 IU/ml) may contribute to the lower antibody responses to conjugate vaccines in older adults.[422] The immunogenicity and the effect on NPC by PCVs in high-risk adults and the elderly require further investigation.

The results of a 7-valent CRM_{197} (cross-reactive material, nontoxic variant of diphtheria toxin isolated from cultures of Corynebacterium diphtheriae strain C7 (β197)) PCV trials in North California and the native American population in Arizona show that the vaccine is very effective in infants, who were immunised at 2, 4, 6 and 12-15 months of age (Table 11). Serotype specific efficacy differs among vaccine serotypes. In the California trial, the immunity for serotypes 9V, 14, 18C and 23F was superior to other vaccine serotypes. The failure to detect significant protection for vaccine serotypes 4, 6B, and 19F may be due to the small number of cases in the control group (48 cases) and in the PCV group (3 cases). Although an increase in non-vaccine serotypes was detected in the Navajo study (but not in the California study), the number of cases of IPD caused by non-vaccine serotypes did not increase in either study. In the California trial, 95% of PCV recipients achieved an antibody level of 0.5 μg/ml.[16] Thus, this level is likely to confer protection against IPD in the population and could be used as a surrogate marker for the efficacy of conjugate vaccines. A recently completed clinical trial in 9480 HIV-infected children in South Africa showed that the efficacy of 9-valent PCV is 50% for bacteraemia and 80% for meningitis in these high-risk children.[423] All the clinical trials are well designed and have an adequate statistical power to detect the outcome in question.

Table 11. Efficacy of 7-valent pneumococcal conjugate vaccine against invasive disease, as reported from randomised trials in the US

Invasive disease	Efficacy % (95%CI)
Vaccine serotypes[16,424]	97.4 (84.4, 99.9) 76.8 (95%CI: 9.4, 95.1)
All serotypes[16]	92.7 (77.0, 98.6)
Bacteraemic pneumonia[16]	85
Vaccine serotypes (cases: controls)[16]	
4 (0:0)	-
6B (7:1)	85.7 (-11.2, 99.7)
9V (3:0)	100 (-142, 100)
14 (11:0)	100 (60.2, 100)
18C (9:0)	100 (49.3, 100)
19F (13:2)	84.6 (32, 98.4)
23F (6:0)	100 (15.1, 100)

Three studies have reported the efficacy of 7-valent PCV against otitis media (Tables 12a-b).[16,17,425] In the two Finnish otitis media trials, the 7-valent PCV prevents 56% to 57% of serotype-specific culture confirmed acute OM and 25% to 34% of any serotypes.[17,18] Cross-reactive immunity was detected for serotype 6A only, not other serotypes belonging to the same serotype in the vaccine. The efficacy of vaccine increases along with the severity of disease, from 6% against all clinical episodes to 20% against ventilatory tube replacement[16] and between 61% and 69% against severe forms of ear disease such as spontaneous perforation or bulging tympanic membrane, caused by vaccine serotypes.[425] A 9-valent CRM_{197} PCV has also been shown to reduce otitis media episodes by 17% in toddlers aged 12 to 35 months in a day care centre in Israel.[19]

Table 12a. Efficacy of 7-valent pneumococcal conjugate vaccine against otitis media of any aetiology

Otitis media	Efficacy % (95%CI)		
	US study[16,426]	**Israeli study[19]**	**Finnish study[17]**
Visits	8.9 (5.8, 11.8)	-	-
Episodes	7.0 (4.1, 9.7)	17*	-
Frequent otitis media 4/5	11.9 (1.6, 21.1)	-	-
Ventilatory tube replacement	20 (1.5, 35.2)	-	-
AOM of any aetiology	6 (-4, 16)	-	6 (-4, 16)

** 95% CI not available*

Table 12b. Efficacy of 7-valent pneumococcal conjugate vaccine against pneumococcal otitis media

Otitis media	Efficacy % (95%CI) Finnish studies	
	Study 1[17]	**Study 2[18,425]**
Vaccine serotypes	57 (44, 67)	56 (44, 66)
Vaccine serotypes (spontaneous perforation)	-	69 (5, 90)
Vaccine serotypes (sponatanous perforation and bulging tympanic membrane)	-	61 (44,73)
Vaccine serogroups	51 (27, 67)	-
Culture-confirmed pneumococci	34 (21, 45)	25 (11, 57)

The California trial suggests that PCV appears to be effective in preventing pneumonia in infants and young children.[16] The reported vaccine efficacy was 11.4% (95%CI: 1.3, 20.5) for clinical pneumonia, 33% (95%CI: 7.3, 51.5) for X-ray-confirmed pneumonia, 73.1% (95%CI: 38, 88.3) for consolidation ($\geq$2.5cm on X-ray) and 85% for bacteraemic pneumonia (Table 13). The 9-valent PCV has been shown to reduce the occurrence of respiratory infections by 15% to 16% in young children attending day care in Israel[19] and pneumonia by 17% in HIV-infected children in South Africa.[423]

Evaluation of efficacy of PCVs against acute pneumococcal OM and non-invasive disease needs further determination. In addition, the development of standard diagnostic criteria for pneumonia is essential in generating comparable data for the impact of PCVs on culture-negative pneumonia.

Table 13. Efficacy of 7-valent pneumococcal conjugate vaccine against pneumonia and other respiratory infections

Basic for diagnosis	Efficacy % (95% CI)
US study[426]	
Clinical diagnosis	10.7 (-0.7, 20.8)
Chest X-ray confirmed	35.0 (5.5, 55.8)
Consolidation on chest X-ray ($\geq$2cm)	62.7 (11.3, 84.3)
Israeli study[19]	
Upper respiratory infection	15
Lower respiratory infection	16

PCVs have been shown to reduce the carriage rate for vaccine serotypes, particularly antibiotic resistant serotypes (6B, 9V, 14, 19A (19F), 23F)[50,406] in vaccinated children and their contacts.[427] A trial in South Africa reported a 50% reduction in penicillin resistant pneumococci, 21% carriage in immunised infants compared with 41% in controls.[406] In addition, PCV has been reported to reduce antibiotic use, a 5.3% in the

California trial[16] and antibiotic days, a 17% in day care attendees in Israel.[19] Therefore, PCVs have the potential to reduce the prevalence of resistant strains and antibiotic use.

Studies in the US[428], Israel,[410] South Africa[406] and The Gambia[429] have shown that PCVs reduce the acquisition of NPC of vaccine serotypes in immunised children although an increase in colonisation with non-vaccine serotypes has also been detected.[17,79,406,428,430] In The Gambia trial, non-vaccine serotypes were 79% in the 7-valent PCV recipients compared with 42.5% in controls.[429] A trial of 9-valent conjugate vaccine found that carriage of non-vaccine serotypes was 39% in immunised children and 21% in the controls in Israel, with a significant increase in serotypes 7 and 15,[406] which are known to be important cause of IPD.[309]

The Finnish otitis media trial also detected a 33% increase in disease caused by non-vaccine serotypes in the 7-valent PCV recipients.[17] It is uncertain whether these data indicate true serotype replacement, or the "unmasking" of less prevalent serotypes due to elimination of predominant serotypes by conjugate vaccine. However, a community-randomised trial in Native American Indian[428] and mathematical modelling data[431-433] suggest that conjugate vaccination results in true replacement of carriage of non-vaccine serotypes. Although replacement in carriage of non-vaccine serotypes and an increase in culture confirmed OM caused by non-vaccine serotypes occurred in vaccinated infants, there was no evidence of an increase in IPD caused by non-vaccine serotypes.[16] These data highlight uncertainty in the long-term effectiveness of PCVs and the need to develop effective and affordable pneumococcal vaccines.

The results from clinical trials suggest that PCV provides at least 4 years immunity[16] but the duration of protective immunity remains to be determined. Data from Hib conjugate vaccine indicates that conjugate vaccines could provide long-term immunity.[392] Continuous surveillance following widespread use of PCV in infants and long-term follow-up of vaccinated adults with high-risk conditions are necessary to determine the duration of its effectiveness.

In the US[2] and Canada,[71] the recommended schedule for newborns is four doses, administered at 2, 4, 6 and 12 to 15 months of age. Depending on the age, one or more dose of vaccine are also recommended for children between the ages of 24 months and 59 months with high-risk conditions. In the UK, PCV is recommended in children less than two years of age with certain high-risk conditions, one each at 2, 3, and 4 months of age or two doses at least a month apart if aged 5 to 24 months.[21] Further studies are required to determine the optimal schedule for newborns and among persons above 2 years of age, the effectiveness of fewer doses, the requirement for periodic boosting with conjugate or polysaccharide vaccine, the benefits of sequential vaccination with PCV and PPV and the identification of immune markers that correlate with clinical protection.

1.2.1.2.3. Protein pneumococcal vaccines

Five antigens of pneumococcal proteins, neuraminidase, autolysin, pneumolysin, pneumococcal surface protein A (PspA) and pneumococcal surface adhesin A (PsaA or 37-kDa) are considered as potential candidate vaccines.[434] In addition to protection against all pneumococcal serotypes, these protein antigens appear to elicit a T-cell-dependence with immunological memory.[435,436] In animal models immunisation with pneumolysin and PspA have been shown to protect against pneumococcal disease.[437-439] Conjugation of these proteins to capsular polysaccharide could also enhance the immunogenicity and efficacy of the vaccine in high-risk adults and the elderly.[434] Current data indicate that PspA appears to protect against IPD[436] and PsaA protects against carriage.[440] Therefore, both proteins can be recommended for inclusion in the formulation of protein vaccine.[436] Since these vaccines are more likely to be affordable for widespread use in developing countries, their development should be encouraged. Further studies are also required to determine the ability of these proteins to combat a variety of existing pneumococcal serotypes that cause the various clinical syndromes.

1.2.2. Cost-effectiveness of pneumococcal vaccination

1.2.2.1. Pneumococcal polysaccharide vaccine

Studies in North America and Europe show that pneumococcal polysaccharide vaccination is cost-effective in preventing pneumococcal pneumonia or IPD or penicillin resistant pneumococcal infection, particularly in the elderly (Table 14). A recent study in five European countries, including Scotland, Belgium, France, Spain and Sweden, found that pneumococcal vaccination in all persons 65 years of age and above is cost-effective for preventing IPD.[441] Under certain assumptions vaccination is cost saving.[442] Most studies have used the following basic assumptions for determining cost-effectiveness: (a) 15% to 50% of pneumonia are caused by the pneumococcus (b) 75% to 80% of cases of pneumococcal pneumonia are caused by organisms of serotypes included in the vaccine, (c) 50% to 80% vaccine efficacy (assuming vaccine is effective in preventing both bacteraemia and non-bacteraemic serious pneumococcal disease), (d) 3 to 8 years of immunity, (e) $15 for a vaccine (1983 cost).[443] However, it is important to acknowledge that current evidence on the clinical effectiveness of pneumococcal polysaccharide vaccination is limited to the prevention of pneumococcal bacteraemia. In the absence of direct evidence on preventing non-bacteraemic pneumonia, the validity of these cost-effectiveness studies remains uncertain.

Table 14. Economic studies of pneumococcal polysaccharide vaccine

Investigator	Year	Vaccine	Location	Risk group	Outcome measure	Cost-effective[3]
[1]OTA[444]	1979	14-valent	US	Elderly	Pneumococcal pneumonia*	Yes
Willems et al[445]	1980	14-valent	US	Elderly	Pneumococcal pneumonia*	Yes
Sisk & Riegelman[446]	1986	23-valent	US	Elderly	Pneumococcal pneumonia*	Yes
Gable et al[447]	1990	23-valent	US	Elderly	Pneumococcal pneumonia*	Yes
Holzer et al[448]	1993	23-valent	US	Elderly	Pneumococcal pneumonia*	Yes
Plans et al[449]	1995	23-valent	Spain	Elderly	Pneumococcal pneumonia*	Yes
Jimenez & Gullar[450]	1996	23-valent	Spain	Elderly	Pneumococcal pneumonia*	Yes
Baltussen et al[451]	1997	23-valent	Netherlands	Elderly	Pneumococcal pneumonia*	Yes
Sisk et al[442]	1997	23-valent	US	Elderly	Invasive disease***	Yes
Gable et al[452]	1997	23-valent	US	Elderly	Pneumococcal pneumonia*	Yes
Herman et al[443]	1998	23-valent	US	Elderly	Penicillin resistance pneumococcal infection	Yes
De Wals[453]	1999	23-valent	Canada	Elderly and adults with CMC[2]	Pneumococcal pneumonia*	Yes
Nichol et al[357]	1999	23-valent	US	Adults with COPD****	Pneumococcal pneumonia*	Yes
Pepper et al[454]	2000	23-valent	US	Marine corps	Pneumococcal pneumonia*	Yes
Ament et al[441]	2000	23-valent	Five European regions **	Elderly	Invasive disease***	Yes
Ament et al[455]	2001	23-valent	Europe	Elderly	Invasive disease Non-bacteraemic pneumococcal pneumonia	Yes

COPD = chronic obstructive pulmonary disease
* Pneumococcal pneumonia (bacteraemic and non-bacteraemic pneumococcal pneumonia)
** Europe (including Scotland)
*** Invasive disease (pneumococcal bacteraemia and meningitis)
**** Also received influenza vaccine
[1] US Congressional Office of Technology Assessment (OTA)
[2] CMC (chronic medical conditions)
[3] Cost-effectiveness varied according to outcome measures used. These included direct and indirect medical costs, societal costs or both medical and societal costs and also the value of costs per life-year saved/gained among countries

1.2.2.2. Pneumococcal conjugate vaccine

Two US economic studies have suggested that routine use of PCV in infants and young children is likely to be cost-effective.[456,457] One study concluded that the prevention of IPD alone has been estimated to gain net direct costs of $0.08 to $2.42 per child.[456] Vaccination against invasive and non-invasive pneumococcal disease with a vaccine price of $58 per dose has been estimated to cost society $80,000 per life-year saved, $160 per otitis media episode, $3200 per pneumonia case, $15,000 per bacteraemia case and $280,000 per meningitis case prevented.[457] The investigators conclude that if the vaccine price was lower, it could even be cost saving.[457] However, these data cannot be extrapolated to countries with different health care systems such as the UK. Economic analysis of pneumococcal conjugate vaccination programme in the UK has not yet been established. The results of the analysis can provide a rationale and justification for introducing PCV into the UK primary immunisation programme.

1.2.3. Issues in relation to use of polysaccharide vaccine

In the UK, a single dose of PPV is currently recommended for individuals aged two years and above with certain chronic medical conditions (Table 15). The vaccine is not yet recommended for all elderly and residents in long stay facilities as in the US.[1] So far, little is known about the factors associated with adherence to vaccination guidelines, views on vaccine indications and responsibilities among clinicians in the UK.

Table 15. Indications for pneumococcal polysaccharide vaccine

UK[458]
Chronic cardiac disease
Chronic pulmonary disease
Chronic liver disease (including cirrhosis)
Chronic renal disease (including nephrotic syndrome)
Diabetes mellitus
Hyposplenism (including homozygous sickle cell disease)
Immunodeficiency states (including HIV infection)
US (additional indications)[1]
Aged 65 years and above
All residents of nursing homes, homes for the aged, chronic care facilities or wards
Alcoholism

Surveys from England showed that coverage of vaccine is low but it is increasing, from 4% in 1995[13] to 15% in 1998[14] among persons with vaccine indications. This indicates that the acceptance of the vaccine among health care professionals and patients is poor in the UK. Data on the number of doses of PPV distributed in the UK and other parts of Europe have reported to be increasing.[15] These increases may be associated with changes in recommendations for pneumococcal vaccination policies in these countries,[15] suggesting that a national guideline is influential in improving vaccine coverage. The monitoring of the numbers of vaccine doses used and distributed are required to identify the areas in need of improvement in vaccine delivery and utilisation in primary care and hospital care settings in Scotland.

Lack of awareness of vaccine availability and its benefits are reported to be the major reasons for not being vaccinated in 73% of patients with indications for PPV in the UK.[14] Similarly, 57% of the elderly aged 65 years and above reported "not knowing vaccination was needed" as the most common reason for not receiving the vaccine in the US national survey.[459] Other reasons for not receiving the vaccine may partly relate to controversy regarding its side effects, efficacy, duration of protection and failure to consider vaccination during patient appointments.[460-462] Since knowledge, attitudes and practice of health care professionals and patients are known to affect the acceptance of vaccine,[463] studies in these areas and the reasons for receipt and non-receipts of vaccine in high-risk patients are required in Scotland.

A UK study reported that 85% of PPV recipients received vaccine on the basis of advice from their GPs,[14] indicating the pivotal influence of the primary care team in determining vaccine coverage. Organised education and vaccination programmes for PPV in England have been shown to increase vaccine coverage from 4% to 33%.[13] Similar strategies are reported to improve the rate of pneumococcal polysaccharide vaccination in the US[464-467] and Belgium.[337]

Currently, no financial support is available for GPs to use PPV in Scotland. The presence of reimbursement and the adoption of age-based policies analogous to influenza vaccination[468] could enhance coverage of PPV. Studies in the US show that the use of computer, chart, letter and label to identify vaccine eligible patients, standing orders for nurses, information leaflets on disease and the benefits and side effects of vaccination, can improve coverage of vaccine in high-risk patients.[469,470]

The evidence indicates that about 70% of patients admitted to hospital with pneumococcal pneumonia or bacteraemia had previous hospital admissions.[471-474] This suggests that previous hospital care could be used to identify persons at increased risk for pneumococcal disease.[475,476] The organised hospital based programmes in outpatient, emergency departments and geriatric units have been shown to improve coverage of PPV among high-risk patients.[477-484] However, only 0.5% of patients with indications for PPV vaccine had received the vaccine in a hospital care setting in the UK.[14] Thus, research on factors influencing PPV use and the presence of vaccination policies in clinical settings is required to modify any problems in the delivery of vaccine to high-risk patients.

2. AIMS OF THE STUDY

The aim of the thesis was to determine the burden and epidemiology of pneumococcal disease and the characteristics of pneumococcal polysaccharide vaccination practices in Scotland. This should inform future public health policy decisions on preventing pneumococcal disease in Scotland, in particular in relation to the role of pneumococcal polysaccharide and conjugate vaccines.

The specific objectives were:

1. Burden of invasive pneumococcal disease

- To determine the incidence of invasive pneumococcal disease in children, the elderly and other age groups;
- To assess the prevalence of penicillin and erythromycin non-susceptibility of invasive isolates;
- To evaluate the relative contribution of the pneumococccus to bacterial meningitis and invasive non-meningitic bacterial disease (INMD), compared with the meningococcus, *Haemophilus influenzae*, group B streptococcus and *Listeria monocytogenes* before and after the implementation of Hib conjugate vaccine into the primary childhood immunisation programme.

2. To estimate coverage of pneumococcal vaccine for serotypes associated with disease and antibiotic non-susceptibility

- To analyse the distribution of serotypes among all invasive and non-invasive pneumococcal isolates and among those shown antibiotic resistance;
- To estimate the coverage of 23-valent and previous 14-valent polysaccharide and 7-, 9- and 11-valent conjugate pneumococcal vaccines for serotypes associated with disease (in order to predict the likely impact on incidence of invasive and non-invasive pneumococcal disease);
- To estimate the coverage of 23-valent and previous 14-valent polysaccharide and 7-, 9- and 11-valent conjugate pneumococcal vaccines for serotypes associated with antibiotic non-susceptibility (in order to predict the likely impact on prevalence of antibiotic resistance in pneumococci).

3. Pneumococcal polysaccharide vaccination practices in Scotland

- To examine knowledge, attitudes and practice of pneumococcal polysaccharide vaccination in general practitioners and hospital doctors;
- To determine pneumococcal polysaccharide vaccine distribution and use in primary care, hospital settings and nursing homes;
- To estimate the coverage of pneumococcal polysaccharide vaccine in high-risk patients.

3. STUDY METHODOLOGY

3.1. Study area

3.1.1. Scotland

For health administration purposes, Scotland is divided into 15 National Health Service boards (HB). These include Argyll and Clyde, Ayrshire and Arran, Borders, Dumfries and Galloway, Fife, Forth Valley, Greater Glasgow, Grampian, Highland, Lanarkshire, Lothian, Orkney, Shetland, Tayside and Western Isles. Scotland has an estimated population of 5.1 million, which represents 8.6% of the UK population. The monitoring and surveillance of pneumococcal disease in Scotland is carried out by the Scottish Centre for Infection and Environmental Health (SCIEH) and the Scottish Meningococcus and Pneumococcus Reference Laboratory (SMPRL), both located in Glasgow.

3.1.2. SCIEH and SMPRL

SCIEH operates as a national surveillance centre for monitoring infectious diseases and environmental hazards. Reports from laboratories throughout Scotland are received weekly at SCIEH. Before entering into an electronic dataset, these data are reviewed by a consultant epidemiologist to ensure the accuracy of records. Laboratory reports of pneumococcal disease from 1983 onwards are available in electronic format at SCIEH.

SMPRL has been established to provide an enhanced diagnostic and national surveillance for pneumococcal diseases in 1992. It serves as the national reference laboratory for pneumococcal disease, providing organism confirmation, serotyping and antibiotic susceptibility testing of pneumococcal isolates. All diagnostic laboratories are encouraged to submit isolates from body fluids of patients with suspected pneumococcal disease. However, it is likely that some laboratories only refer isolates thought to be antibiotic resistant. To address this potential bias enhanced active pneumococcal surveillance was established in Scotland in April 1999.

There were 29 to 33 laboratories which reported pneumococcal disease to SCIEH and SMPRL between 1983 and 1999. An increase of 4 reporting laboratories occurred after 1994.

3.2. Population-based laboratory surveillance data

3.2.1. Laboratory records of pneumococcal isolates reported to SCIEH between 1988 and 1999 and the pneumococcal isolates submitted routinely to SMPRL between 1993 and 1999 from all diagnostic laboratories in Scotland have been combined in a single database. Duplicate records of the same patients in SCIEH and SMPRL datasets were identified by matching surname, date of birth, date of specimen, sex, and health board (HB). They were excluded from the study. This dataset was used to examine the serotype distribution in terms of disease presentation, susceptibility for penicillin and erythromycin and the coverage of 23-valent and previous 14-valent polysaccharide and 7-, 9-, and 11-valent conjugate vaccines for both invasive and non-invasive isolates associated with disease and antimicrobial non-susceptibility. Because of the difficulty in determining case ascertainment of non-invasive pneumococcal disease by current laboratory methods, the incidence of disease and the prevalence of penicillin and erythromycin susceptibility were determined only for invasive isolates.

Recurrent disease was considered to be present if the pneumococcus was isolated from the same patient more than 7 days after the initial episode.[94,129] Demographic information on age, sex, site of specimen with date were available in all laboratory records but only limited data for clinical syndrome and outcome of illness.

Laboratory records of invasive pneumococcal, meningococcal, *Haemophilus influenzae*, group B streptococcus (GBS) and *Listeria monocytogenes* isolates reported to SCIEH only between 1983 and 1999 were also reviewed to determine the predominant pathogens responsible for bacterial meningitis and INMD over the period 1983-99. We then compared the data from the two periods, 1983-91 and 1992-99, before and after routine use of Hib conjugate vaccine in October 1992 in Scotland.

The number of laboratories reporting cases of these five pathogens to SCIEH increased in 1983-99; from 29 to 33 for the pneumococcus and meningococcus, from 25 to 28 for GBS and *H. influenzae* and from 15 to 22 for *L. monocytogenes*.

3.2.2. Case definitions

Isolation of pneumococci from a sterile body site was regarded as invasive disease. This included blood, cerebrospinal fluid (CSF), joint or pleural fluid, bone marrow, lung aspirate, pericardial fluid and bronchial aspirate. Bacterial meningitis was defined by the isolation of bacteria from CSF or blood and CSF. Isolates from blood or other normally sterile site but not from CSF were regarded as INMD. Pneumococcal isolates from sputum, nasopharynx, ear, eye, urine and other non-sterile sites were considered as non-invasive disease.

3.2.3. Culture technique used at SMPRL

The identification of pneumococci was performed by latex aggulutination.[485] Pneumococcal isolates were serogrouped/typed by coagglutination testing,[485] using commercially available antisera from the Statens Serum Institut, Copenhagen, Denmark. Additional factor serum was used to classify serotypes of certain serogroups. The Danish system of nomenclature was used to classify serotypes.

Susceptibility testing was started for penicillin in 1992 and for erythromycin in 1994. Minimal Inhibitory Concentrations (MICs) were determined by a standard agar dilution method (incorporating the antibiotic into agar) from 1992 to 1993. The E-test (Cambridge Diagnostics, Cambridge UK) was used from 1994 onwards. The breakpoints for penicillin susceptibility were defined in accordance with the National Committee for Clinical Laboratory Standards (NCCLS).[231] Penicillin sensitivity, intermediate resistance and high-level resistance were defined if isolates had an MIC of $\leq$0.06 μg/ml, between 0.1 and 1 μg/ml and $\geq$2 μg/ml respectively. Isolates in the intermediate and resistant categories were considered non-susceptible to penicillin. A single breakpoint concentration (1 μg/ml) was used to classify susceptible and non-susceptible isolates for erythromycin.

3.2.4. Calculation of incidence of disease and antibiotic non-susceptibility

The appropriate denominators for calculation of all rates for disease and susceptibility for penicillin and erythromycin of invasive isolates were obtained from the Office for National Statistics (ONS) population projections, UK (http://www.statistics.gov.uk). The midpoint year, 1993, was used for calculating the mean age and sex specific rates of disease and antimicrobial non-susceptibility, for a combined pneumococcal dataset from SCIEH and SMPRL between 1988 and 1999.

To calculate the age specific incidence of pneumococcal, meningococcal, *H. influenzae*, GBS and *L. monocytogenes* cases in the SCIEH dataset, the two midpoint years, 1987 and 1996, were used for two time periods (1983-91) and (1992-99) before and after the routine use of Hib vaccine.

3.2.5. Antibiotic prescription

Prescription data for penicillin, erythromycin and all other antimicrobial agents in Scotland between 1992 and 1999 were collected from the Primary Care Unit, Information and Statistics Division (ISD) of the Common Services Agency of the NHS in Scotland. Rates for antibiotic prescribing were calculated per 100,000 population. The association between the prevalence of antimicrobial non-susceptibility and antibiotic prescription rate was examined in 15 HBs.

3.2.6. Statistical analysis

Study data were entered into "DataEase version 4.5" and exported to SPSS version 10 (SPSS Inc, Chicago, Illinois, US). Data analysis for serotypes distribution and their relationships to disease and antimicrobial non-susceptibility was performed in SPSS. 95% confidence intervals for coverage of polysaccharide and conjugate vaccines for invasive disease causing serotypes in different age groups between 1993 and 1999 were calculated in Stata (Stata Corporation, version 6.0, 1999, College Station, Texas). It was assumed that serotypes in a serogroup were potentially cross-reactive (e.g. 6B vs. 6A). Analyses are for complete years 1988-1999, with the exception of serotypes distribution for invasive isolates, which is until August 1999 only.

Relative risk of disease incidence according to sex and corresponding 95% confidence intervals were calculated using the CIA programme (Gardner SB, Winter PD, Gardner MJ: London, 1991). Using SPSS, χ^2 test for trend and Pearson correlation coefficients were used to determine associations between variables, including (1) the annual antibiotic prescription rates for penicillin and erythromycin and their annual prevalence (2) overall antibiotic prescription rates for penicillin and erythromycin and the prevalence of non-susceptibility in HBs, and (3) the annual prescription rate of penicillin, erythromycin, all antibiotics and the prevalence of penicillin non-susceptibility in age groups less than 5 years, 5-64 years and 65 years and above. $P< 0.05$ was regarded as statistically significant.

3.2.7. Data protection issues

Laboratory reports for patients who had invasive bacterial disease due to pneumococcal or the other four pathogens were accessed by the author for the purpose of data analyses only. These data were maintained in accordance with guidelines for patient confidentiality at SCIEH and the Data Protection Act throughout the study period.

3.3. Questionnaire surveys on the epidemiology of pneumococcal vaccination practices

Pneumococcal polysaccharide vaccine is currently recommended for persons with certain underlying medical conditions in the UK. Information on distribution and actual use of pneumococcal vaccine in primary and hospital care settings is not clearly established in Scotland. Little is known about vaccine indications, barriers for vaccine use, policies and responsibilities for vaccination among clinicians. In addition, few data are available on the reasons for receipt and non-receipt of vaccine among high-risk patients. A total of four questionnaire surveys have been conducted to assess the epidemiological features of pneumococcal polysaccharide vaccination in Scotland. The specific surveys were:

Survey 1. Opinions of general practitioners and hospital doctors on pneumococcal polysaccharide vaccination;

Survey 2. Pneumococcal polysaccharide vaccine distribution and use along with practices and policies in primary care and hospital settings;

Survey 3. Pneumococcal polysaccharide vaccine coverage, policies and reasons for receipt and non-receipt of vaccine in nursing homes;

Survey 4. Pneumococcal polysaccharide vaccine coverage and antibiotic prophylaxis together with meningococcal polysaccharide vaccine, Hib conjugate vaccine and annual influenza vaccine (1997, 1998, 1999 and 2000 years) in splenectomised patients;

3.3.1. Ethical approval and co-operation

Surveys 1, 2 and 3 did not require ethical approval. Nevertheless, permission was sought from:

Survey 1: Clinical Medical Directors of hospitals, HDs and GPs.

Survey 2: The ISD Privacy Advisory Committee, Edinburgh, which decided that the selection of 10 high-risk patients per CMR practice does not require ethical approval, since the CMR system does not identify the names of these patients.

Survey 3: The nurse in charge or care manager of nursing homes.

Survey 4: Permission was sought from the Director of Public Health in the 15 HBs to access details of splenectomised patients in their area who were registered at ISD (Appendix a). Agreement was obtained from 11 HBs. Approval from The ISD Privacy Advisory Committee was also obtained (Appendix a).

3.3.2. Survey 1

This survey included 800 current practising GPs and hospital doctors (HDs) who were chosen to be representative of Scotland.[486] The selection and identification of study participants were carried out in September 1999. The names of 400 GPs along with their demographical details were selected from a national database at the ISD of the Common Services Agency, Edinburgh, using computerised random sampling (detail in Appendix b).

Thirty National Health Service (NHS) hospitals were chosen systematically from the NHS hospital directory based on their geographical locations to be representative of Scotland. They were requested to supply details of 25 HDs including names, specialties, grades or positions and corresponding addresses by sampling personnel records. A simple random sample was performed using SPSS random function to select four hundred doctors from 16 hospitals for the survey.

The study questionnaire was based on that of Berk and colleagues.[487] A pilot study was tested on 12 GPs and 12 HDs in October 1999. The questionnaire was then revised. In November 1999, the modified questionnaire was sent to the 800 GPs and HDs. Non-respondents received a reminder questionnaire after six weeks. They were requested to give their views on a number of related issues: the target groups for vaccination, vaccine safety and effectiveness, practice and policies, the source of their knowledge, and any initiatives in place to enhance the use of PPV in their setting (Appendix c).

3.3.3. Survey 2

The distribution of the number of doses of PPV used was reviewed for the whole of Scotland between 1983 and 1999 and for general practices included in the "Continuous Morbidity Recording" (CMR) system between 1993 and 1999. These data were obtained from ISD.

The CMR practices included 53 general practices covering 5% of the population of Scotland. The CMR system requires at least one diagnosis to be recorded at each face-to-face contact between a GP and patient. The diagnoses are Read coded and all data are internally linked to build up a continuous record for each patient. Information collected through CMR system is considered to be representative of the Scottish population in terms of sex, age, deprivation and rural/urban mix and geographic locations.[486] On 1 April 1998, the CMR data became part of the national "core data set". Specific diagnostic codes for chronic medical conditions were used to search for the number of at-risk patients registered in the CMR practices. To avoid counting more than once for high-risk patients, the identification of these patients was based on persons not GP consultations. A questionnaire was sent to GPs in the CMR practices, which asked for the information related to use of PPV.

For the survey, ten high-risk patients per CMR practice were selected and identified by ISD similar to survey one (Appendix b). Since the CMR system is completely anonymous, the names of the patients were not known. Nevertheless, the date of birth, sex and postcode of these patients were available. This information allowed GPs to identify them and their medical records. A pilot study, including 20 patients in two CMR practices, was carried for the validity and suitability for the study design and questionnaire. To compensate the time needed for reviewing and establishing the vaccination status of high-risk patients, a set fee was offered to each GP. They were asked to review the medical records to identify vaccination status, place of vaccination, their views on vaccine indications, policies and responsibilities for vaccination programme (Appendix d).

As in the previous report,[15] the number of doses of PPV dispensed per 10,000 population was used to estimate the use of vaccine. The total number of persons recommended for vaccination in Scotland was also estimated based on the number of registered high-risk patients in the CMR practices. These figures made it possible to estimate the rate of vaccination per 10,000 population for the whole Scotland and the coverage of vaccine in the CMR practices. Data from the survey and vaccine distribution statistics also gave an opportunity to check what proportion of distributed vaccines was actually used in recommended patients in the CMR practices.

The Carstairs Deprivation Score[488] was used to determine the influence of deprivation category of the patient's area of residence on the coverage of vaccine. The level of deprivation was based on the postcode sector, which was categorised into 1 to 7, 1 being the most affluent and 7 being the most deprived.

3.3.4. Survey 3

ISD supplied the directory of all nursing homes in Scotland, which included home name, the corresponding address and bed complement. There were a total of 550 licensed nursing homes in the whole of Scotland in 2001 providing nursing care primarily to the elderly. The questionnaire was piloted to 12 nursing homes and was amended as necessary. All nursing homes were sent a reply-paid questionnaire on 12 June 2001 and were requested to be completed by the nurse in charge or care manager. A reminder was posted to those who did not respond to the initial questionnaire.

The questionnaire requested information on the number of residents, the number of general practices looking after residents, the existence of immunisation records, coverage of vaccine in residents, vaccination policies, the factors influencing coverage of vaccine, and the reasons for receipt and non-receipt of vaccine (Appendix e). The latter two were selected from a number of key reasons defined in a pilot study. Since information was requested in an aggregated format, it was completely anonymous and did not permit the identification of elderly individuals living in each nursing home.

3.3.5. Survey 4

Patients who underwent splenectomy between 1 January 1988 and 31 December 1998 were identified using the Scottish Morbidity Record (SMR01), which is recorded on discharge from hospital for all episodes of inpatient or day-case care. It collects information on demography and the clinical details of patients receiving hospital care. These SMR01 records were linked to the Register General Office, Scotland, for death registrations, using probability matching as described in the previous report,[489] to identify the patients who had died.

GPs of all living patients were identified from Practitioner Services, which provide administrative support and process payments to all Primary Care Practitioners on behalf of Primary Care Trusts and Island Health Boards in Scotland. Since medical records of deceased patients would not be available to GPs, they were excluded from the survey. A pilot study was performed on GPs of 12 splenectomised patients to determine the feasibility and validity of study design and questionnaire.

The appropriate changes were made before sending a questionnaire to GPs of all living splenectomised patients. The questionnaire asked for the information on whether splenectomy was performed as an elective or emergency, the status of antibiotic prophylaxis and vaccination against pneumococcus, meningococcus, Hib and influenza (Appendix f). A reminder was sent to those who did not respond after 6 weeks.

3.3.6. Data analysis

The chi-squared test was used to identify the significance of association between the variables for pneumococcal polysaccharide vaccination in GPs and HDs. The Carstairs Deprivation Score[488] was used to determine the deprivation index values of the patients' area of residence relation to PPV coverage in at-risk patients in the CMR practices and the coverage of vaccines and antibiotic prophylaxis in splenectomised patients.

Since the data are non-Normally distributed, nonparametric tests were applied to the survey of PPV coverage in elderly nursing home residents. In addition, Mann-Whitney tests were used to compare median coverage where the covariate was binary and Kruskal-Wallis tests were used when the covariate had more than two levels. P-value < 0.05 was defined as statistically significant.

4. RESULTS

4.1. Disease burden

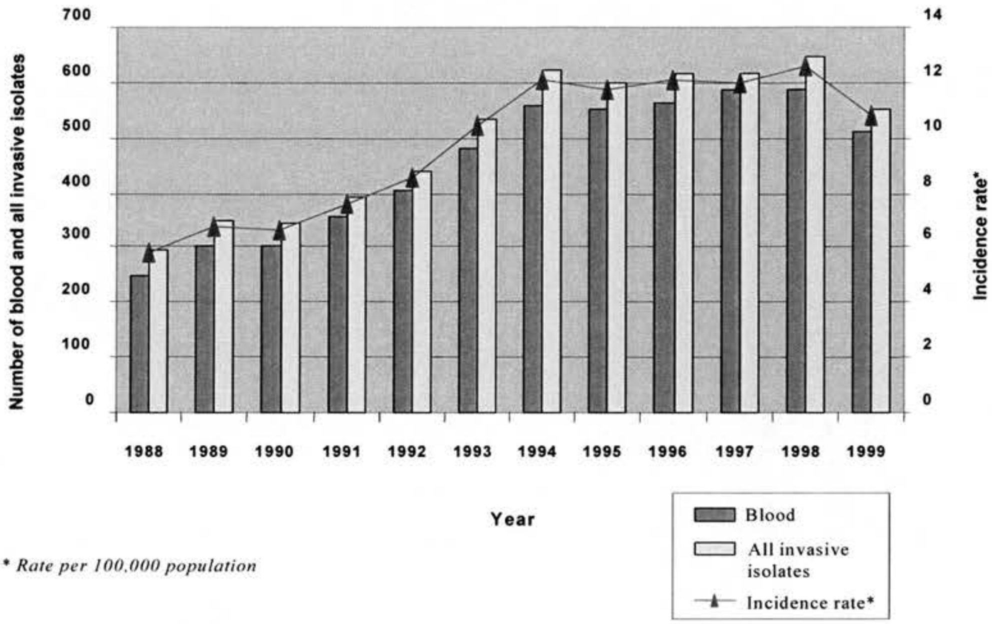
4.1.1. Invasive isolates

There were 6007 reports of invasive pneumococcal disease from a sterile body site (see in section 3.2.2. for case definition) in the study period from 1988 to 1999. 2657 (44.2%) from the age group 65 years and above, 2186 (36.4%), 6-64 years, 734 (12.2%) $\leq$5 years and 430 (7.2%) of unknown age. The age of patients ranged from 0 to 99 years, with a median age of 54 years. 5456 (90.8%) were from blood, 467 (7.8%) from CSF and 84 (1.4%) from other sterile sites (joint or pleural fluid, bone marrow, lung aspirate, pericardial fluid and bronchial aspirate). 3077 (51.2%) were from males, 2758 (45.9%) females and 172 (2.9%) of unknown sex. Antibiotic susceptibility testing against penicillin and erythromycin was performed in only 20.8% and 18.7% respectively.

4.1.2. Incidence of IPD

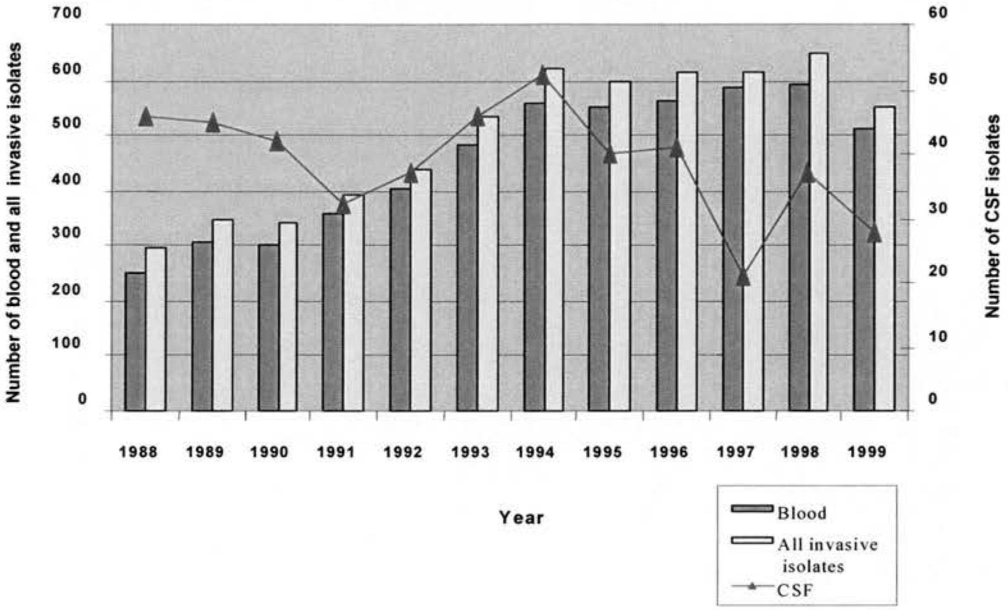
The overall mean annual incidence of IPD was $9.8/10^5$ population between 1988 and 1999, with an increasing trend from 5.8 in 1988 to 12.6 in 1998 and to $10.8/10^5$ population in 1999 (Figure 1a). The incidence of IPD has been relatively stable in the last six years. The observed increase in the incidence of IPD was due to an increased frequency of blood culture over this period, which increased from 248 isolates in 1988 to 510 isolates in 1999. The overall pattern of ratio of blood and CSF isolates also increased over three-fold in the study period, from 5:1 in 1988 to 18:1 in 1999. No increase was observed for CSF isolates (Figure 1b).

Figure 1a. Number of blood and all invasive isolates and incidence of invasive pneumococcal disease in Scotland, 1988-99



* *Rate per 100,000 population*

Figure 1b. Number of invasive pneumococcal isolates (blood, CSF and all invasive isolates) in Scotland, 1988-99



4.1.2.1. Relative importance of the pneumococcus to other pathogens

There were a total of 12108 cases of invasive bacterial disease caused by the pneumococcus, meningococcus, *H. influenzae*, GBS and *L. moncytogenes* in the study period, 1983-99. Of these, 2514(20.8%) were from CSF. The annual relative contribution of meningitis and INMD due to these five pathogens from 1983 to 1999 is presented in Figures 2a and 2b. The proportion and incidence of meningitis and INMD caused by these five pathogens between 1983-91 and 1992-99 are shown in Table 16.

Figure 2a. Proportion of bacterial meningitis caused by the five pathogens in 1983-99

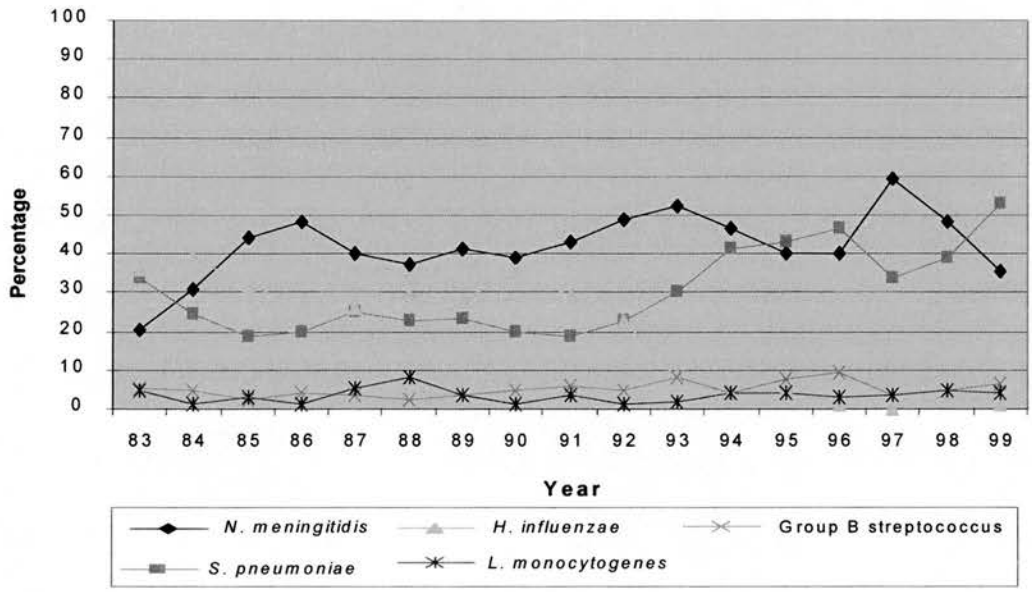


Figure 2b. Proportion of invasive non-meningitic disease caused by the five pathogens in 1983-99

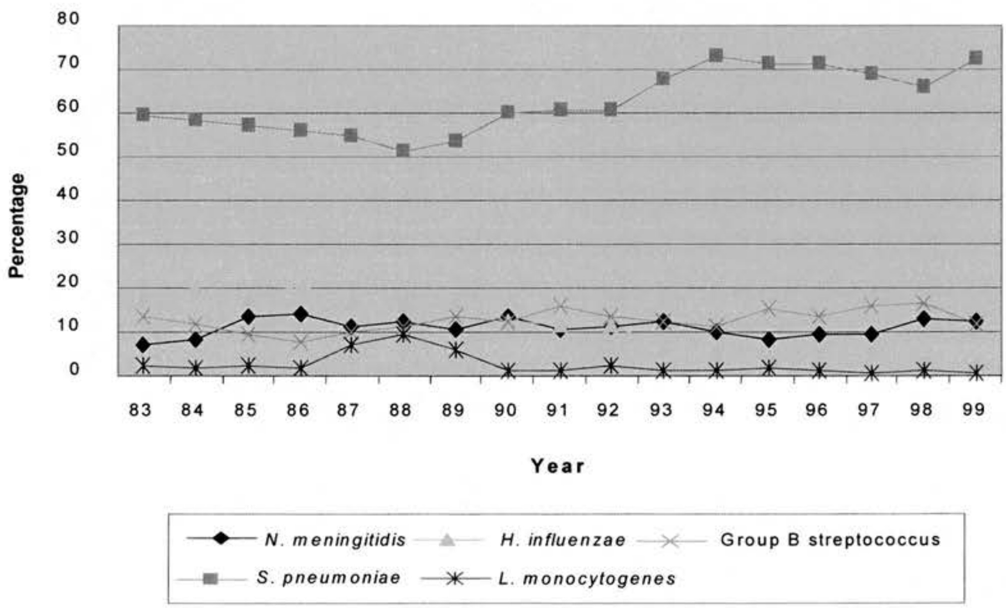


Table 16. Frequency and incidence of bacterial meningitis and invasive non-meningitic disease by pathogen between 1983-91 and 1992-99

	1983-91			1992-99			
Causative pathogens for bacterial meningitis	Number of cases	(%)	Mean annual incidence (per 100,000 population)	Number of cases	(%)	Mean annual incidence (per 100,000 population)	Percent change in disease incidence between (1983-91) and (1992-99)
N. meningitidis	681	39.2	1.5	365	(47)	0.9	-40
S. pneumoniae	389	22.4	0.8	282	(36.3)	0.7	-12.5
H. influenzae	539	31	1.2	61	(7.8)	0.1	-91.7
Group B streptococcus	68	3.9	0.1	47	(6.1)	0.1	0
L. monocytogenes	60	3.5	0.1	22	(2.8)	0.05	-50
Total	1737	(100)	3.8	777	(100)	1.9	-50
Causatives pathogens for non-meningitic disease							
N. meningitidis	507	(11.4)	1.1	555	(10.8)	1.4	+27.3
S. pneumoniae	2518	(56.7)	5.5	3540	(68.7)	8.6	+56.4
H. influenzae	732	(16.5)	1.6	280	(5.4)	0.7	-56.3
Group B streptococcus	520	(11.7)	1.1	711	(13.8)	1.7	+54.5
L. monocytogenes	167	(3.7)	0.4	64	(1.3)	0.2	-50
Total	4444	(100)	9.7	5150	(100)	12.6	+29.9

4.1.2.1.1. Age-specific incidence of invasive bacterial disease by pathogen

The age-specific incidence rates for meningitis and INMD varied with pathogens in 1983-91 and 1992-99 (Tables 17a-b). There was a 50% decrease (from 3.8 to 1.9 per 100,000 population) in the incidence of bacterial meningitis and a 30% increase (from 9.7 to 12.6 per 100,000 population) in the INMD in 1983-91 and 1992-99 caused by these five pathogens. The pneumococcus was the most common cause of INMD and the second most common cause of meningitis between 1983-91 and 1992-99. During these two periods, the incidence decreased 12.5% (0.8 to 0.7 per 100,000 population) for meningitis and increased 56% (5.5 to 8.6 per 100,000 population) for INMD caused by the pneumococcus.

Those under the age of 5 years showed the greatest increase in the proportion of cases of meningitis and INMD due to the pneumococcus between the periods 1983-91 and 1992-99. An increase of 2 to 3-fold in the proportion of bacterial meningitis due to the pneumococcus was noted in age groups, less than 1 year and 1-4 years. The proportion of INMD disease caused by the pneumococcus also increased in all age groups except for the 5-24 years age group. A substantial proportion of bacterial meningitis in each period (63.6% and 82.8% respectively) and (78% in the second period) and INMD was caused by the pneumococcus in the elderly, (67% in the first period and 78% in the second) respectively.

Table17a. Proportion of bacterial meningitis caused by five pathogens during the period 1983-91 and 1992-99 by age groups

Pathogens / Age groups	Period	*N. meningitidis* Cases	(%)	Incidence*	*S. pneumoniae* Cases	(%)	Incidence*	*H. influenzae* Cases	(%)	Incidence*	Group B streptococcus Cases	(%)	Incidence*	*L. monocytogenes* Cases	(%)	Incidence*
<1 year	1983-91	184	(36.1)	31.2	71	(13.9)	12	184	(36.1)	31.2	53	(10.4)	9	17	(3.3)	2.9
	1992-99	109	(48.9)	23.2	58	(26.0)	12.4	15	(6.7)	3.2	37	(16.6)	7.9	4	(1.7)	0.9
1-4 years	1983-91	218	(38.8)	9.4	44	(7.8)	1.9	293	(52.2)	12.7	0	(0)	0	6	(1.1)	0.3
	1992-99	108	(57.1)	5.3	46	(24.3)	2.3	34	(18)	1.7	0	(0)	0	1	(0.5)	0.05
5-14 years	1983-91	81	(58.7)	1.4	37	(26.8)	0.6	20	(14.5)	0.3	0	(0)	0	0	(0)	0
	1992-99	38	(73.1)	0.7	11	(21.2)	0.2	2	(3.8)	0.04	0	(0)	0	1	(1.9)	0.02
15-24 years	1983-91	103	(82.4)	1.3	18	(14.4)	0.2	3	(2.4)	0.04	1	(0.8)	0.01	0	(0)	0
	1992-99	52	(76.5)	1	15	(22.1)	0.3	1	(1.5)	0.02	0	(0)	0	0	(0)	0
25-44 years	1983-91	28	(32.9)	0.2	42	(49.1)	0.3	8	(9.4)	0.06	4	(4.7)	0.03	3	(3.5)	0.02
	1992-99	21	(29.2)	0.2	42	(58.3)	0.3	3	(4.2)	0.02	4	(5.6)	0.03	2	(2.8)	0.02
45-64 years	1983-91	32	(22.5)	0.3	90	(63.4)	0.9	5	(3.5)	0.05	3	(2.1)	0.03	12	(8.5)	0.1
	1992-99	24	(31.2)	0.3	43	(55.8)	0.5	3	(3.9)	0.03	2	(2.6)	0.02	5	(6.5)	0.05
≥65 years	1983-91	9	(9.0)	0.1	67	(67.0)	1	4	(4)	0.06	3	(3)	0.04	17	(17)	0.3
	1992-99	9	(11.0)	0.1	64	(78.0)	1	0	(0)	0	0	(0)	0	9	(11)	0.1
N/A	1983-91	26	(30.2)	0.1	29	(33.7)	0.1	22	(25.6)	0.05	4	(4.7)	0	5	(5.8)	0
	1992-99	4	(28.6)	0	3	(21.4)	0	3	(21.4)	0	4	(28.6)	0	0	(0)	0
All ages	1983-91	681	(39.2)	1.5	389	(22.4)	0.8	539	(31)	1.2	68	(3.9)	0.1	60	(3.5)	0.1
	1992-99	365	(47.0)	0.9	282	(36.3)	0.7	61	(7.8)	0.1	47	(6.1)	0.1	22	(2.8)	0.05

**** Rate per 100,000 population, N/A = data not available***

Table 17b. Proportion of invasive non-meningitic disease caused by five pathogens during the period 1983-91 and 1992-99 by age groups

Pathogens / Age groups	Period	*N. meningitidis* Cases	(%)	Incidence*	*S. pneumoniae* Cases	(%)	Incidence*	*H. influenzae* Cases	(%)	Incidence*	Group B streptococcus Cases	(%)	Incidence*	*L. monocytogenes* Cases	(%)	Incidence*
<1 year	1983-91	109	(17.7)	18.5	119	(19.3)	20.2	161	(26.1)	27.3	192	(31.2)	32.6	35	(5.7)	5.9
	1992-99	100	(21.1)	21.3	114	(24.1)	24.3	31	(6.6)	6.6	223	(47.1)	47.5	5	(1.1)	1.1
1-4 years	1983-91	175	(22.7)	7.6	219	(28.5)	9.5	369	(47.9)	16	5	(0.6)	0.2	2	(0.3)	0.1
	1992-99	161	(40.8)	7.9	174	(44.2)	8.5	57	(14.5)	2.8	2	(0.5)	0.1	0	(0)	0
5-14 years	1983-91	61	(32.8)	1.1	89	(47.8)	1.5	34	(18.3)	0.6	2	(1.1)	0.03	0	(0)	0
	1992-99	82	(50.3)	1.6	61	(37.4)	1.2	14	(8.6)	0.3	5	(3.1)	0.1	1	(0.6)	0.02
15-24 years	1983-91	69	(29.9)	0.9	102	(44.2)	1.3	14	(6.1)	0.2	29	(12.5)	0.4	17	(7.3)	0.2
	1992-99	97	(42.5)	1.9	94	(41.2)	1.8	7	(3.1)	0.1	28	(12.3)	0.5	2	(0.9)	0.04
25-44 years	1983-91	14	(3.5)	0.1	240	(60.0)	1.9	32	(8)	0.2	78	(19.5)	6.1	36	(9)	0.3
	1992-99	36	(6.1)	0.3	419	(70.4)	3.4	23	(3.9)	0.2	111	(18.6)	0.9	6	(1)	0.05
45-64 years	1983-91	27	(4.1)	0.3	528	(79.4)	5.3	34	(5.1)	0.3	59	(8.9)	0.6	17	(2.5)	0.2
	1992-99	28	(3.0)	0.3	740	(79.8)	7.8	45	(4.9)	0.5	99	(10.7)	1	15	(1.6)	0.2
≥65 years	1983-91	24	(1.9)	0.4	1058	(83.6)	15.7	48	(3.8)	0.7	103	(8.1)	1.5	33	(2.6)	0.5
	1992-99	35	(1.7)	0.6	1753	(82.8)	28	95	(4.5)	1.5	200	(9.4)	3.2	34	(1.6)	0.5
N/A	1983-91	28	(9.0)	0.1	163	(52.6)	0.4	40	(12.9)	0.1	52	(16.8)	0.1	27	(8.7)	0.06
	1992-99	16	(6.3)	0.04	185	(73.1)	0.4	8	(3.2)	0.02	43	(17.0)	0.1	1	(0.4)	0
All ages	1983-91	507	(11.4)	1.1	2518	(56.7)	5.5	732	(16.5)	1.6	520	(11.7)	1.1	167	(3.7)	0.4
	1992-99	555	(10.8)	1.4	3540	(68.7)	8.6	280	(5.4)	0.7	711	(13.8)	1.7	64	(1.3)	0.2

**** Rate per 100,000 population, N/A = data not available***

4.1.3. Sex-specific incidence

The incidence of IPD (bacteraemia and meningitis) was higher in males than females. The overall incidence for bacteraemia was $9.4/10^5$ in males and $8.1/10^5$ population in females (male:female = 1.2:1) (RR = 1.17, 95%CI 1.11, 1.24) for bacteraemia. The overall incidence for meningitis in males and females was $0.9/10^5$ and $0.6/10^5$ population (male:female = 1.5:1) (RR = 1.41, 95%CI 1.18, 1.70). There was a higher incidence of bacteraemia in males than females for all age groups except 10-14 years (Figure 3a). The incidence of pneumococcal meningitis was also higher in males than females for all age groups except in adults 35-44 years, 55-74 years and 85 years and above (Figure 3b). The annual incidences of bacteraemia and meningitis were also higher in males than females between 1988 to 1999 (except for years 1993 and 1996 for meningitis and 1994 for bacteraemia).

Figure 3a. Incidence of pneumococcal bacteraemia by age group in Scotland, 1988-99

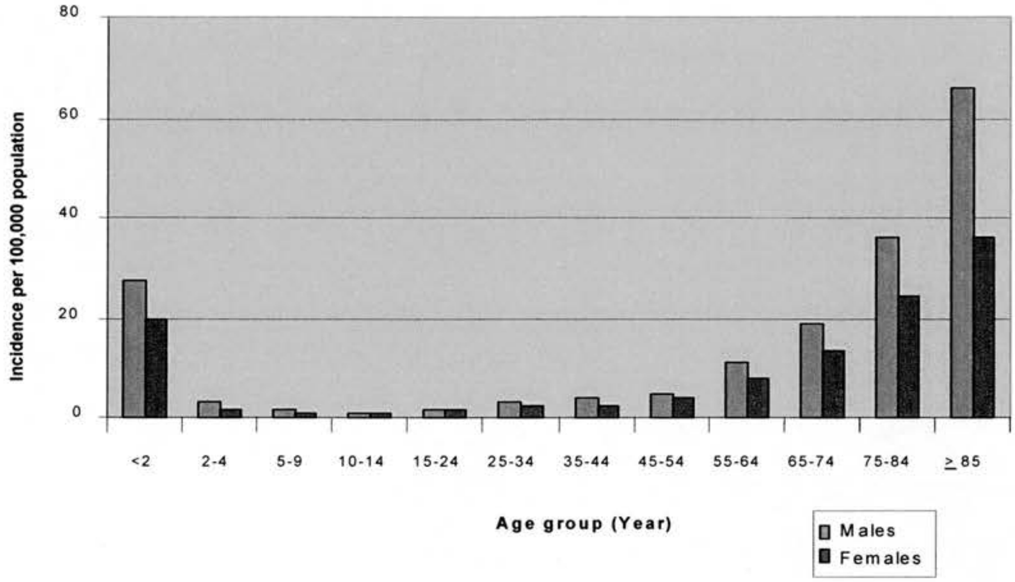
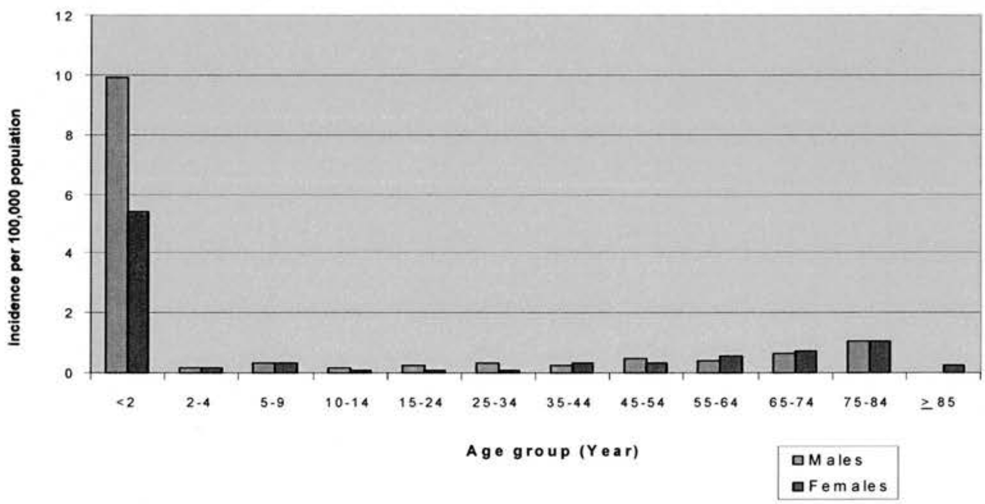


Figure 3b. Incidence of pneumococcal meningitis by age group in Scotland, 1988-99

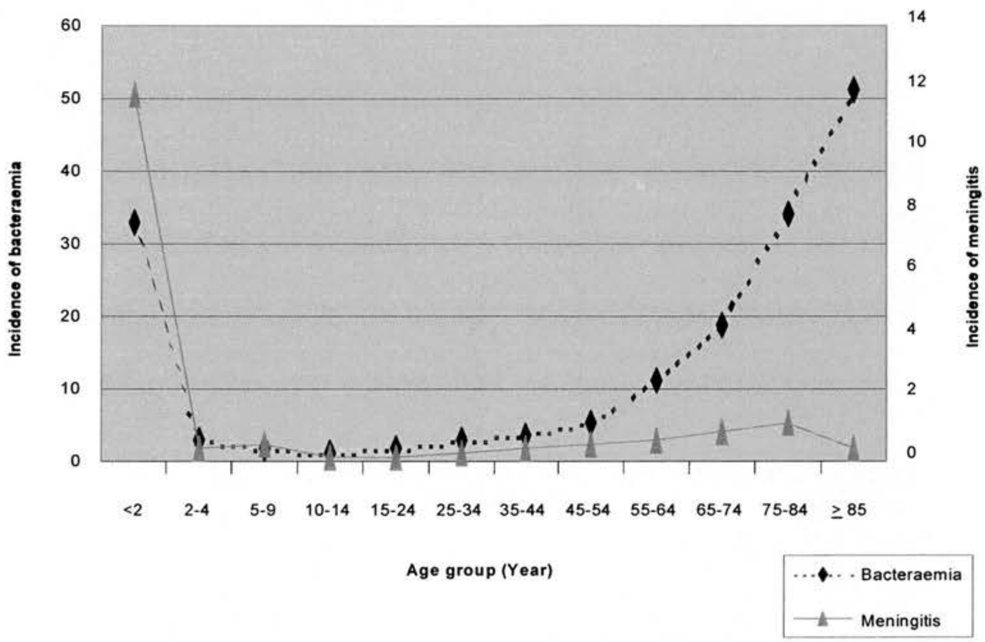


4.1.4. Age-specific incidence

The highest incidence of IPD occurred in infants aged less than two years, $44.9/10^5$ persons and the elderly aged 65 years and above, $28.4/10^5$ persons (Figure 4). The incidence for bacteraemia was $9/10^5$ population in all ages but increased to $33.1/10^5$ persons infants aged less than two years and to $27.5/10^5$ persons in the elderly, 65 years and above. Marked increases in bacteraemia were observed in infants, from 16.9 in 1988 to $47.4/10^5$ persons in 1999, and the elderly, from 14.5 in 1988 to $31.2/10^5$ persons in 1999.

The number of blood isolates increased in different age groups from 1988 to 1999; from 20 to 56 in less than 2 years, from 26 to 66 in 5 years and less, from 99 to 192 in 5-64 years, and from 114 to 245 in 65 years and above. An overall trend towards on increased ratio for blood to CSF isolates was also observed from 1988 to 1999 for these age groups, with the corresponding figures of from 2.2:1 to 2.8:1, from 2.9:1 to 3:1, from 3.7:1 to 10.7:1 and from 12.7:1 to 28.7:1. However, there was no increase in the number of CSF isolates in age groups, less than 2 years, less than 5 years, 5-64 years and 65 years and above in the study period.

Figure 4. Age-specific incidence of pneumococcal bacteraemia and meningitis, 1988-99

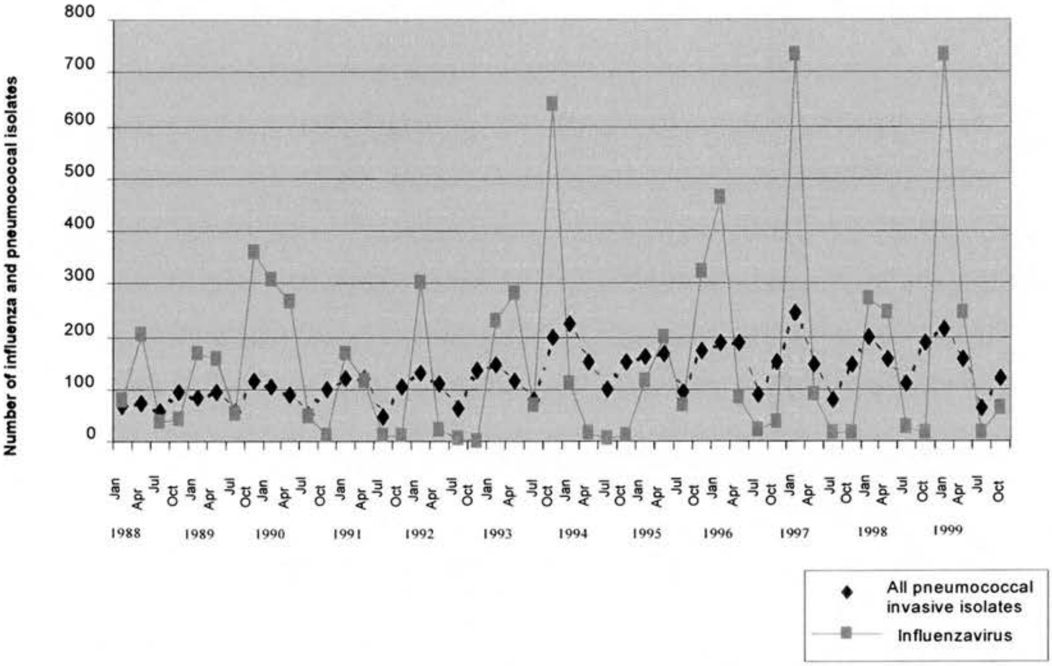


The incidence of meningitis was $0.8/10^5$ population at all ages. The highest incidence was noted in children aged less than two years, $11.8/10^5$ persons, but decreased substantially to $0.4/10^5$ persons in age group, two to four years. The incidence of meningitis ranged from 0.4 to $1.2/10^5$ persons in aged 65 years and above.

4.1.5. Seasonal variation

A seasonal trend in the occurrence of IPD was observed. Data aggregated in three-month periods over the study period showed that the number of cases consistently peaked in the first three months of the year. This pattern coincided with the clear seasonal pattern of influenza activity reported to SCIEH by laboratory records (Figure 5).

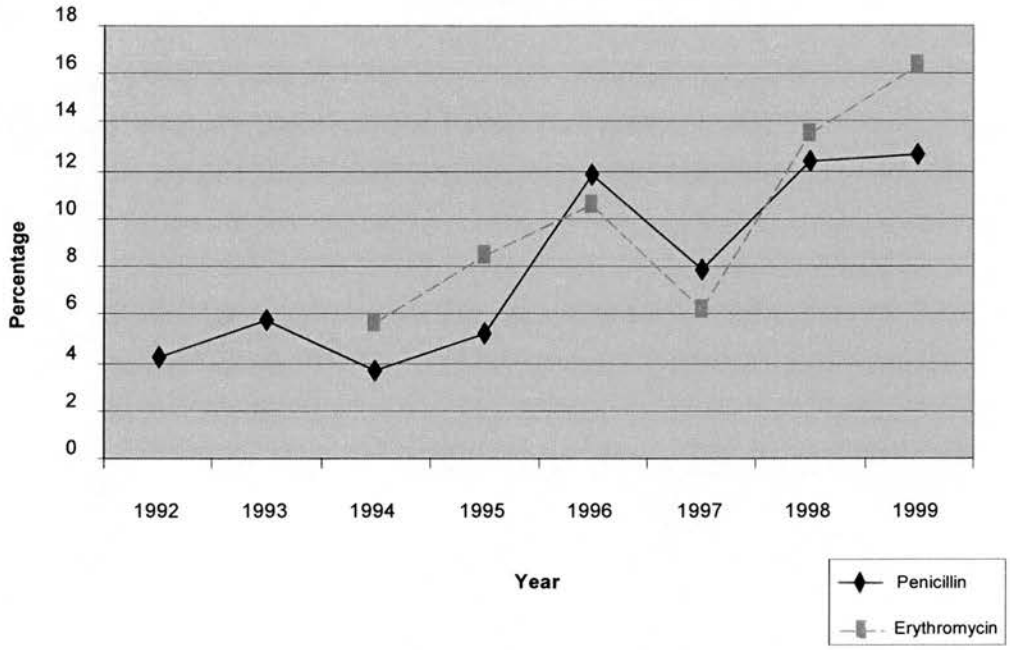
Figure 5. Seasonal pattern of laboratory reports of influenza and invasive pneumococcal isolates by 3-month period, Scotland, 1988-99



4.1.6. Antibiotic susceptibility

The overall proportion of non-susceptibility was 8.6% for penicillin in 1992-99 and 9.6% for erythromycin in 1994-99 among invasive isolates tested for antibiotic susceptibility. Penicillin non-susceptible isolates increased from 1 (4.2%) in 1992 to 21(12.6%) in 1999 ($p = 0.0004$) and erythromycin resistant isolates from 7 (5.6%) in 1994 to 27 (16.3%) in 1999 ($p = 0.0015$) (Figure 6). Only 2 cases of penicillin-resistant pneumococci were reported (in 1998).

Figure 6. Proportion of penicillin (1992-99) and erythromycin (1994-99) non-susceptible isolates among all invasive pneumococcal isolates



4.1.7. Age-specific antibiotic susceptibility

There was an inconsistent increase in the proportion of penicillin non-susceptible invasive isolates in age groups, less than 5 years, 5-64 years and 65 years and above between 1992 and 1995 but an increase trend was observed from 1996 onwards in these three age groups (Figures 7a-c). The overall prevalence of penicillin non-susceptible isolates was 3.7% in age group less than 5 years, 7.3% in age group 5-64 years and 8.6% in age group 65 years and above.

Figure 7a. Prevalence of penicillin non-susceptible pneumococcal isolates in age group less than 5 years, 1992-99

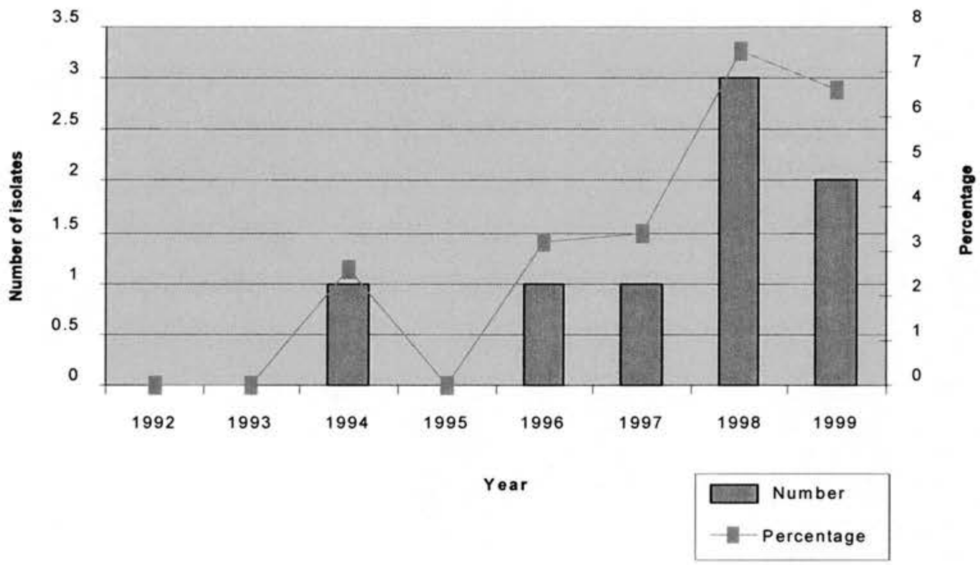


Figure 7b. Prevalence of penicillin non-susceptible pneumococcal isolates in age group 5-64 years, 1992-99

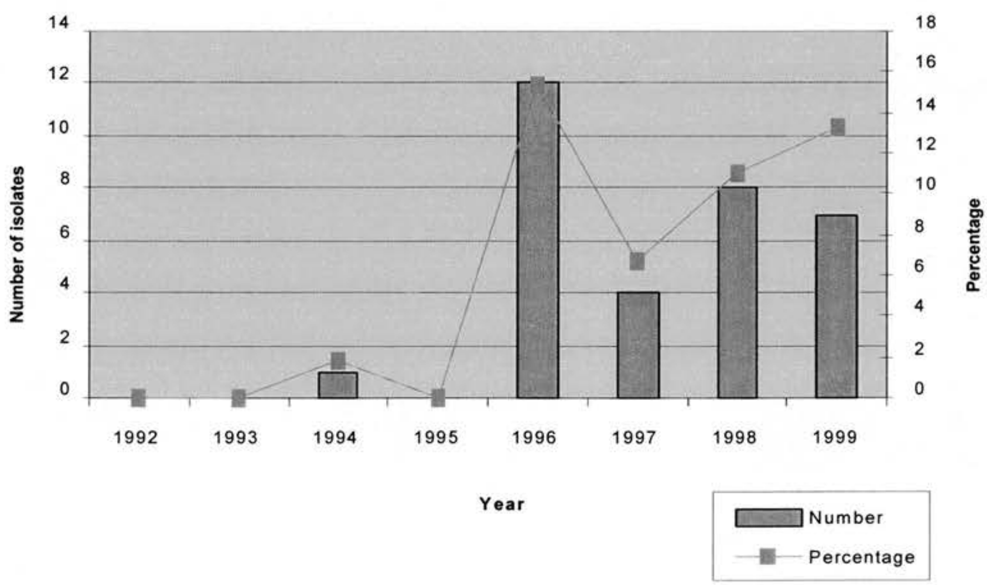
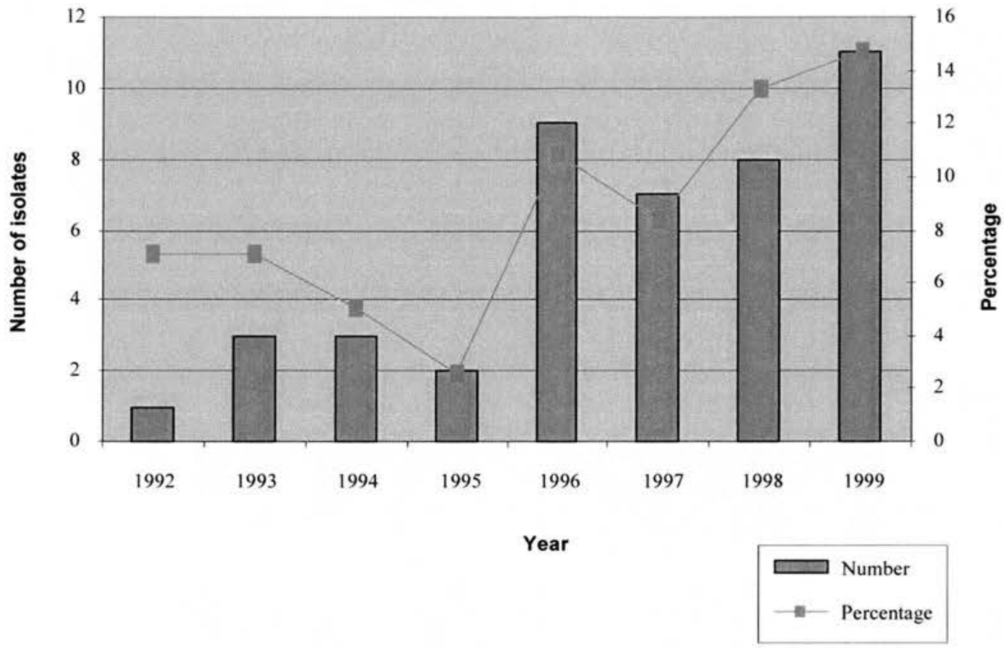


Figure 7c. Prevalence of penicillin non-susceptible pneumococcal isolates in age group 65 years and above, 1992-99



4.1.8. Antibiotic susceptibility and antibiotic prescribing

Geographical variations in the proportion of penicillin non-susceptibility correlated marginally with penicillin prescribing rates in each health board (Pearson correlation, r = 0.52, p = 0.05). No correlation was documented for erythromycin prescription rate and the incidence of erythromycin non-susceptible isolates (r = 0.385, p = 0.16) (Table 18). A scatter plot was constructed before the assessment for these correlations.

A statistically significant correlation was noted between the prevalence of pencillin non-susceptible isolates and the annual rates of penicillin, erythromycin and all antibiotics dispensed in Scotland in 1992-1999 for age groups less than 5 years (p = 0.004, 0.002 and 0.009, respectively) and 65 years and above (p= 0.021, 0.026 and 0.013 respectively). However, in the age group 5-64 years, a correlation was documented between the prevalence of penicillin non-susceptibility and the rate of erythromycin prescription (p= 0.013), but not for pencillin (p = 0.153) and all antibiotics prescription (p = 0.056).

Table 18. Geographic variation in pneumococcal penicillin and erythromycin non-susceptibility and the pattern of penicillin and erythromycin prescribing, 1988-99

	Penicillin sensitivity (1992-99) * Number (%)				Rate per 10^5 population (per year)		Erythromycin sensitivity (1994-99)*** Number (%)			Rate per 10^5 population (per year)	
Area	S	I	R	Total	Penicillin non-susceptible isolates**	Penicillin prescriptions per 10^5 population per year	S	R	Total	Erythromycin non-susceptible isolates****	Erythromycin prescriptions per 10^5 population per year
AC	41(73.2)	15(26.8)	0(0)	56(100)	0.4	24.6	50(94.3)	3(5.7)	53(100)	0.1	5.9
AA	77(91.7)	6(7.1)	1(1.2)	84(100)	0.2	22.9	52(89.7)	6(10.3)	58(100)	0.3	5.6
BR	12(80)	2(13.3)	1(6.7)	15(100)	0.4	21.2	6(100)	0(0)	6(100)	0	5.6
DG	3(30)	7(70)	0(0)	10(100)	0.6	21.7	6(75)	2(25)	8(100)	0.2	3.7
FF	7(70)	3(30)	0(0)	10(100)	0.1	23.5	8(88.9)	1(11.1)	9(100)	0.1	6.1
FV	46(93.9)	3(6.1)	0(0)	49(100)	0.1	21.4	35(89.7)	4(10.3)	39(100)	0.3	5.5
GR	10(76.9)	3(23.1)	0(0)	13(100)	0.1	22.1	5(45.5)	6(54.5)	11(100)	0.2	6.4
GG	318(87.1)	47(12.9)	0(0)	365(100)	0.7	28	279(91.5)	26(8.5)	305(100)	0.5	7.6
LN	221(96.5)	8(3.5)	0(0)	229(100)	0.2	27.6	178(88.6)	23(11.4)	201(100)	0.7	7.3
LO	333(97.7)	8(2.3)	0(0)	341(100)	0.1	23.4	263(90.4)	28(9.6)	291(100)	0.6	5.9
OR	0(0)	0(0)	0(0)	0(0)	0	20.7	0(0)	0(0)	0(0)	0	5.4
SH	0(0)	0(0)	0(0)	0(0)	0	20.9	0(0)	0(0)	0(0)	0	6.3
TY	25(92.6)	2(7.4)	0(0)	27(100)	0.1	23.8	21(87.5)	3(12.5)	24(100)	0.1	5.7
WI	4(100)	0(0)	0(0)	4(100)	0	18.6	3(75)	1(25)	4(100)	0.6	5.8
HG	42(100)	0(0)	0(0)	42(100)	0	21.4	37(88.1)	5(11.9)	42(100)	0.4	5.6
Scotland	1139(91.5)	104(8.4)	2(0.2)	1245(100)	0.3	24.8	943(89.7)	108(10.3)	1051(100)	0.4	6.3

*S = sensitive, I = intermediate, R = resistance, *=3 patients did not have area locations, ** resistant isolates = non-susceptible (intermediate and resistance), ***=2 patients did not have area locations, **** resistant isolates = non-susceptible, Rate = per 10^5 population per year*

AC = Argyll & Clyde, AA = Ayrshire & Arran, BR = Borders, DG = Dumfries & Galloway, FF = Fife, FV = Forth Valley, GG = Greater Glasgow, GR = Grampian, HG = Highland, LN = Lanarkshire, LO = Lothian, OR = Orkney, SH = Shetland, TY = Tayside, WI = Western Isles

4.2. Pneumococcal polysaccharide vaccination surveys

Although PPV has been available for use in the UK since 1979, the UK Joint Committee on Vaccination and Immunisation (JCVI) did not recommend its use in high-risk groups until 1992. This section presents the data on the epidemiological characteristcs of PPV distribution and use in Scotland based on the four questionnaire surveys. These involve:

4.2.1. Survey 1: Opinion of general practitioners (GPs) and hospital doctors (HDs)

This survey was conducted to determine GPs and HDs knowledge, attitudes and practices in relation to pneumococcal polysaccharide vaccination in order to identify the barriers that may affect vaccine use.

Of the 800 questionnaires sent out, 504 (63%) were returned. Of these, 20 were unanswered because the intended recipient had moved or did not want to participate. Of the 484 (60%) completed questionnaires, 286 (59%) were from GPs and 198 (41%) from HDs. The characteristics of respondents by healthcare setting are shown in Table 19.

Table 19. Characteristics of questionnaire respondents

General practitioners (n=286)	Number (%)
Patient population	
Mean number of patients per practice	5127
Mean number of registered elderly patients ($\geq$65 years) per practice	386
Practice type	
Group	239(84)
Single	47(16)
Practice location	
Rural	42(15)
Urban	244(85)
Hospital doctors (n=198)	**Number (%)**
Grades	
Consultant	39(20)
Specialist Registrar	39(20)
Registrar	42(21)
Senior Registrar	40(20)
House Officer	38(19)
Specialties	
Cardiology	18(9)
Respiratory	20(10)
Renal	21(10)
Endocrine	23(12)
Gastroenterology	21(11)
Oncology	23(12)
Accident and Emergency	27(13)
Geriatric/ Elderly	21(11)
General medicine	24(12)

4.2.1.1. Target groups and knowledge of vaccine

The respondents' views on pneumococcal vaccination in various high-risk conditions are shown in Table 20. Splenic dysfunction and older age were considered to be the most and the least important indication for vaccination, respectively.

Table 20. Views of respondents on indications for pneumococcal polysaccharide vaccination in various high-risk patient groups, by level of agreement

General practitioners (GPs) (n= 286) Hospital doctors (HDs) (n=198)							
Risk conditions	Respondents	Strongly agree %	Agree %	Disagree %	Strongly disagree %	Don't know %	Not Reported %
Splenic dysfunction*	GPs	80	19	0	1	0	0
	HDs	67	14	2	1	16	0
Chronic pulmonary disease*	GPs	59	36	1	1	2	1
	HDs	34	40	5	1	20	0
Immunocompromised*	GPs	51	33	5	1	8	2
	HDs	36	32	6	3	22	1
Chronic heart disease*	GPs	39	39	11	1	9	1
	HDs	21	40	11	1	27	0
Chronic renal disease*	GPs	36	40	10	1	13	0
	HDs	20	35	10	1	33	1
Diabetes mellitus*	GPs	36	40	10	1	13	0
	HDs	14	38	15	1	32	0
Chronic liver disease*	GPs	30	39	13	1	16	1
	HDs	17	39	11	1	31	1
Elderly ($\geq$65 years) (residents of long stay facility)	GPs	15	34	28	5	16	2
	HDs	13	39	18	3	25	2
All elderly $\geq$65 years	GPs	16	31	32	8	12	1
	HDs	10	36	22	4	27	1

** Currently recommended by the UK Departments of Health*

HDs were less likely than GPs to agree on the need for vaccination in the high-risk conditions currently recommended by the Department of Health (DoH). They were also more likely to be uncertain whether the risk condition cited was an indication for vaccine recommendation.

Knowledge of vaccine safety and effectiveness for the patient categories given was suboptimal among respondents (Table 21).

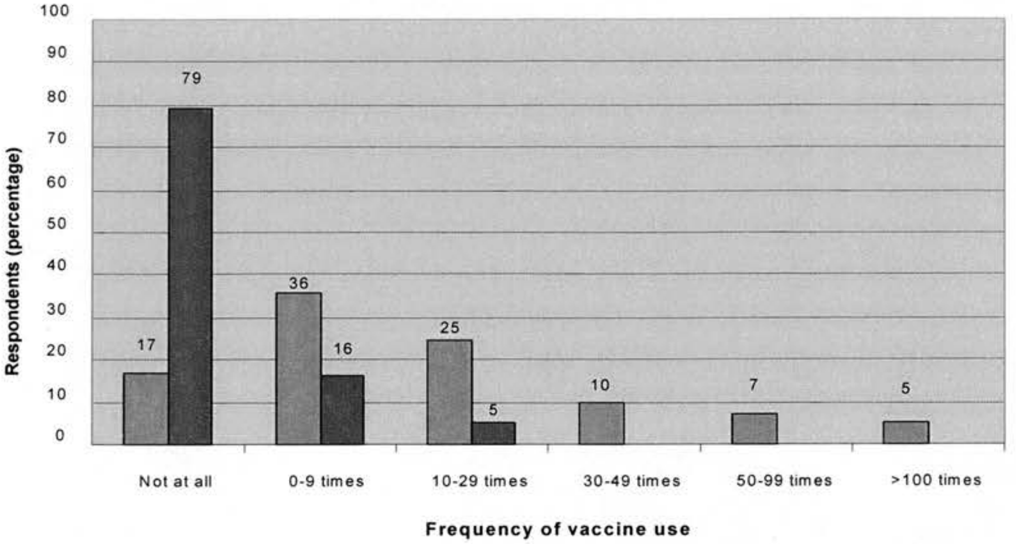
Table 21. Views of respondents on pneumococcal polysaccharide vaccine safety and effectiveness in preventing invasive pneumococcal disease, by patient group, by level of agreement

General practitioners (GPs) (n = 286) Hospital doctors (HDs) (n=198)							
Category	Respondents	Strongly agree %	Agree %	Disagree %	Strongly disagree %	Don't know %	Not reported %
Immunocompromised adults	GPs	28	46	5	2	18	1
	HDs	17	38	4	1	38	2
Adults with chronic heart/pulmonary/renal/ liver/diabetic disease	GPs	25	60	3	1	11	0
	HDs	13	40	4	1	42	0
Elderly (≥65 years)	GPs	20	45	11	2	20	2
	HDs	12	36	6	2	43	1
Young adults	GPs	22	39	7	4	28	0
	HDs	16	34	7	3	40	0

4.2.1.2. Usage

A majority of HDs (79%) had never used the vaccine compared with only 17% of GPs (Figure 8). There was no difference in use of vaccine between specialities or grades of HDs.

Figure 8. Use of pneumococcal polysaccharide vaccine among respondents in the past year



Number of respondents: GPs = 282, HDs = 196

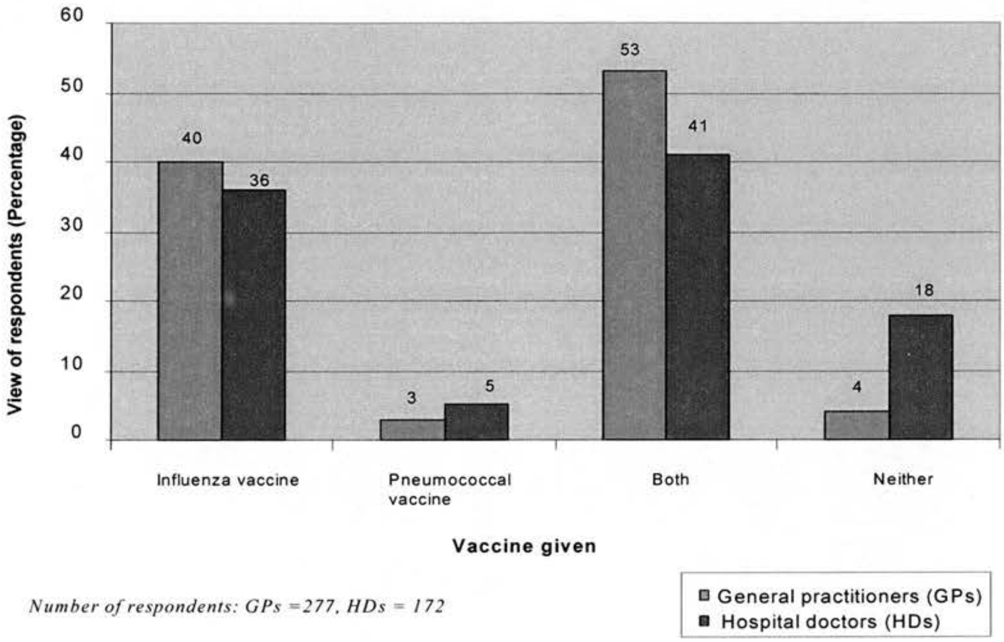
Although statistically not significant, GPs in rural areas and in group practices used more vaccines than single practices and GPs in urban areas (rural = 35/40 (88%) vs urban = 199/242 (82%), p = 0.55) (group practices = 199/235 (85%) vs single practices = 35/47 (74%), p = 0.09).

4.2.1.3. Attitudes and practices

A total of 53% of GPs and 41% of HDs indicated that they would use both influenza and pneumococcal polysaccharide vaccines if an elderly person requested a vaccine against pneumonia (Figure 9). Although influenza vaccine alone would be recommended by 36-40% of GPs and HDs, less than 10% would agree to give PPV alone. GPs in urban areas were more likely to offer both pneumococcal polysaccharide and influenza vaccines (rural = 21/117 (18%) vs urban = 125/141

(89%), p = 0.0001) and those in rural areas were more likely to use influenza vaccine alone (rural = 96/117 (82%) vs urban = 16/141 (11%), p = 0.0001).

Figure 9. Response to elderly patients' requests for vaccination against pneumonia



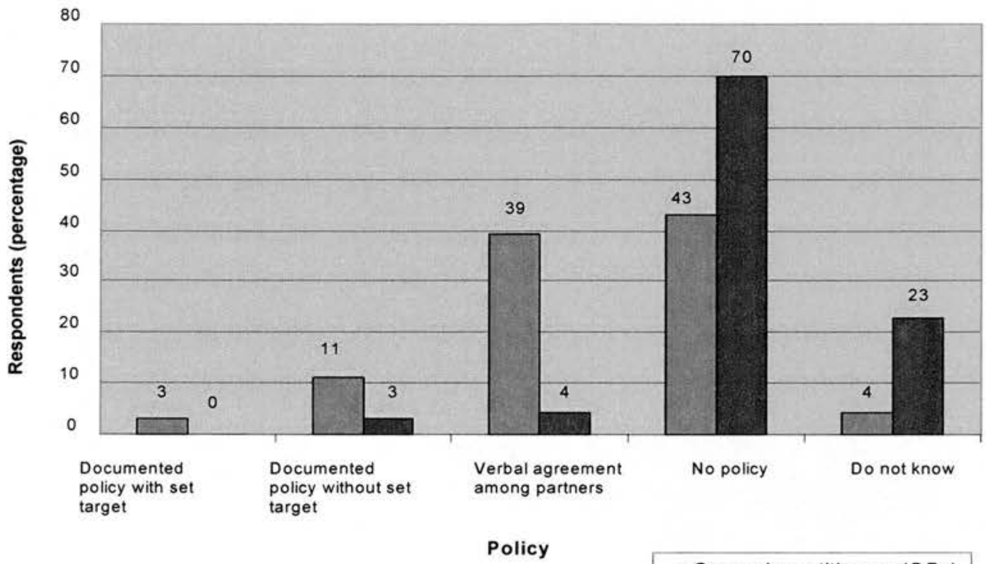
Number of respondents: GPs =277, HDs = 172

Although not statistically significant, use of vaccine varied with practice type. GPs in group practices were more likely to recommend influenza vaccine alone (group practices = 99/216 (46%) vs single practice = 13/42 (31%), p = 0.08) or both pneumococcal polysaccharide and influenza vaccines (group practices = 117/216 (54%) vs single practices = 29/42 (69%), p = 0.08) than those in single practices. Usage of vaccine among HDs did not vary with their grade and specialty.

4.2.1.4. Policies and responsibilities

The presence of policies for pneumococcal vaccination in the respondent's setting is presented in Figure 10. A majority of respondents indicated no pneumococcal vaccination policy in the clinical setting. Only 3% of GPs had a policy, which included a set target.

Figure 10. Reported pneumococcal polysaccharide vaccine policies among respondents

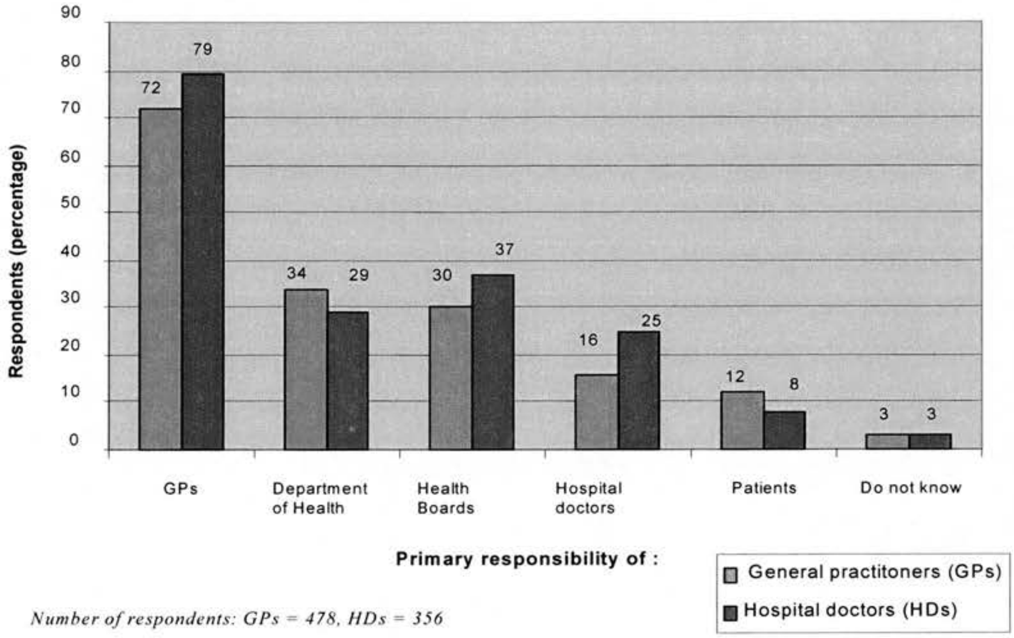


Number of respondents: GPs =276, HDs = 165

Policies for pneumococcal vaccination were associated with general practice type and location with GPs in urban areas (rural = 25/41 (61%) vs urban = 113/226 (50%), p = 0.19) and group practices (group practices = 124/229 (54%) vs single practices = 23/47 (49%), p = 0.51) more likely to have some form of pneumococcal vaccination policy than those in rural and single practices.

Views on the primary responsibility for pneumococcal vaccination among respondents are displayed in Figure 11. The majority (over 70%) of GPs and HDs felt that the primary responsibility for pneumococcal vaccination should be placed with GPs, followed by the DoH and the HBs.

Figure 11. Views on the primary responsibility for pneumococcal polysaccharide vaccination



Number of respondents: GPs = 478, HDs = 356

4.2.1.5. Source of knowledge and strategies for improving vaccine coverage

Discussion with colleagues, personal review of medical literature, past experience and the DoH constituted the most frequently stated main sources of information on PPV both among GPs and HDs (Table 22). Consultants and specialist registrars mostly acquired knowledge of PPV from past experience and further education whereas HDs in other grades gained from other categories.

Table 22. Sources of knowledge about pneumococcal polysaccharide vaccine among respondents: numbers of GPs/HDs noting each source

Source*	General practitioners (n=562) %	Hospital doctors (n=368) %
Discussion with colleagues	43	27
Own review of medical literature	38	33
Past experience	27	26
Department of Health	27	32
Health Boards	22	27
Further medical education	22	28
Advice from manufacturer	14	5
Do not know	5	7

* Can answer more than one category

Most GPs and HDs (80%) considered a clear immunisation policy to be a key strategy for improving vaccine coverage in high-risk patients, followed by financial support for vaccination, promoting public health pneumococcal vaccination campaigns and a computerised system to identify persons with definite indications for the vaccine (Table 23).

Table 23. Strategies to improve pneumococcal polysaccharide vaccine coverage: numbers of GPs/HDs reporting each category

Strategy*	General practitioners (n=948) %	Hospital doctors (n=630) %
A clear immunisation policy	87	80
Financial support for vaccination	72	54
Computerised systems to identify high-risk patients	49	47
Vaccine awareness public health campaign	46	46
Further education on immunisation	32	44
Conclusive evidence of vaccine efficacy	22	30
Nurse assistant	18	16
Do not know	5	3

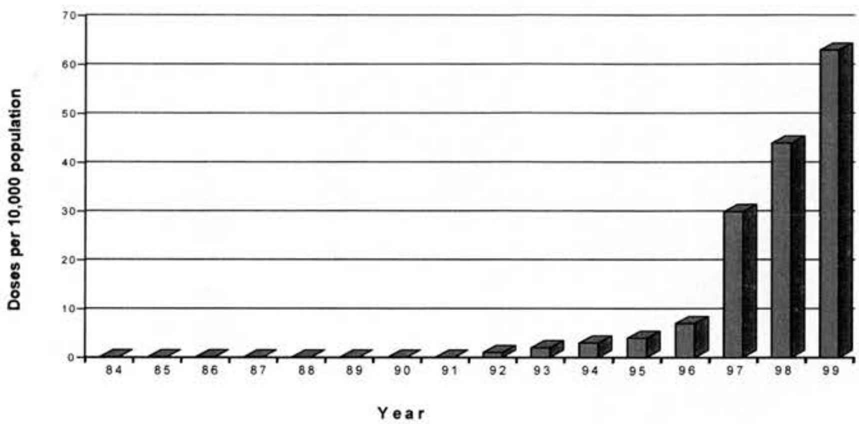
* Can answer more than one category

4.2.2. Survey 2: Pneumococcal polysaccharide vaccine distribution and use in primary care and hospital care settings

Currently PPV is recommended for patients aged two years and above with with splenic dysfunction, chronic heart, lung, liver and renal diseases, diabetes and immunocompromised conditions in the UK.[458] This survey was carried out to examine the distribution patterns and actual use of PPV among high-risk patients in primary care and hospital care settings. In addition, views on vaccine indications, policies and responsibilities for pneumococcal polysaccharide vaccination among GPs in the CMR practices were examined.

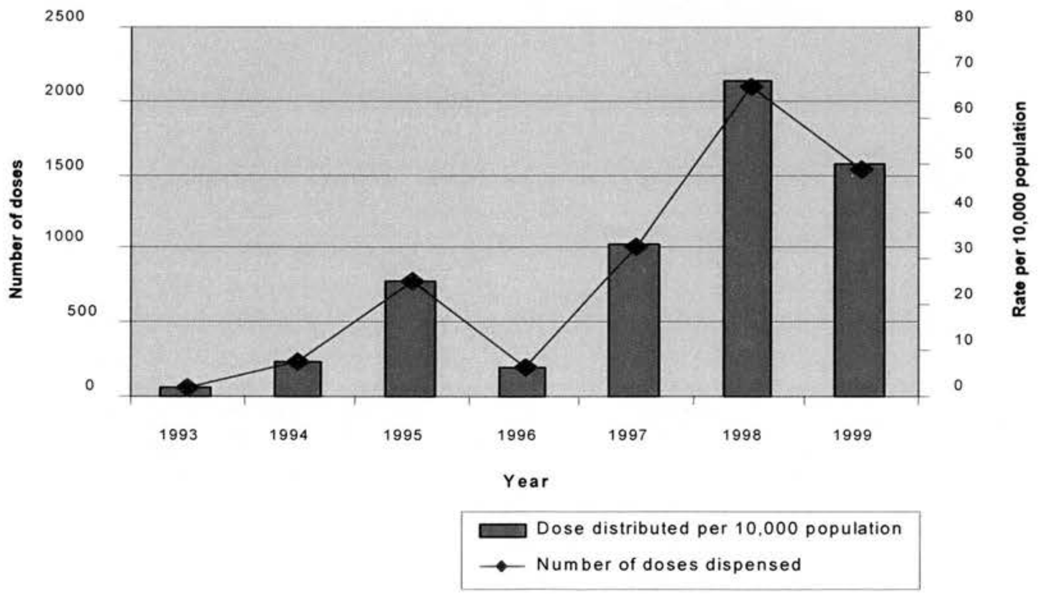
There was a significant increase in the annual distribution of PPV in Scotland in 1984-99 (Figure 12) and in the CMR practices in 1993-99 (Figure 13). Of the 53 questionnaires posted to GPs within the CMR practices, the completed questionnaire was returned by 84.9% (45/53) of GPs. The selected high-risk patients included in the questionnaire survey divided into 8 groups (Table 24).

Figure 12. Annual number of pneumococcal polysaccharide vaccine doses distributed per 10,000 population in Scotland, 1984-99



Vaccine prescription data obtained from the Information and Statistics Division of the Common Services Agency, Edinburgh, Scotland

Figure 13. Number of doses of pneumococcal polysaccharide vaccine dispensed in the 53 CMR practices, 1993-99



Vaccine prescription data obtained from the Information and Statistics Division of the Common Services Agency, Edinburgh, Scotland

Table 24. Pneumococcal polysaccharide vaccine coverage in high-risk patients

High-risk conditions	View on vaccination		Total	Coverage in all ages %	(95% CI)	Coverage in ≤ 64 years of age**	Coverage in ≥ 65 years of age**
	No	Yes					
Chronic pulmonary disease*	216	23	239	9.6	(6, 14)	4	25.4
Chronic heart disease*	93	17	110	15.5	(9, 22)	8.3	18.9
Chronic liver disease*	6	1	7	14.3	(0.4, 58)	0	33.3
Chronic renal disease*	6	0	6	0	(0, 41)	0	0
Diabetic mellitus*	53	14	67	20.9	(12, 33)	15.6	25.7
Asplenic disorders*	6	1	7	14.3	(0.4, 58)	20	16.7
Elderly (65 years of age and above)	126	36	162	22.2	(16, 29)		
Elderly (75 years of age and above)	64	18	82	21.9	(14, 33)		
Overall coverage for conditions indicated by the DoH	380	56	436	12.8	(9, 16)		
Overall coverage for all high-risk conditions	506	92	598	15.4	(12, 18)		

CI = confidence interval

** Recommend by the DoH (current vaccine policy also includes patients with immunodeficiency or immunosuppression)*

*** Included patients with more than one high-risk condition*

4.2.2.1. Distribution and vaccine coverage

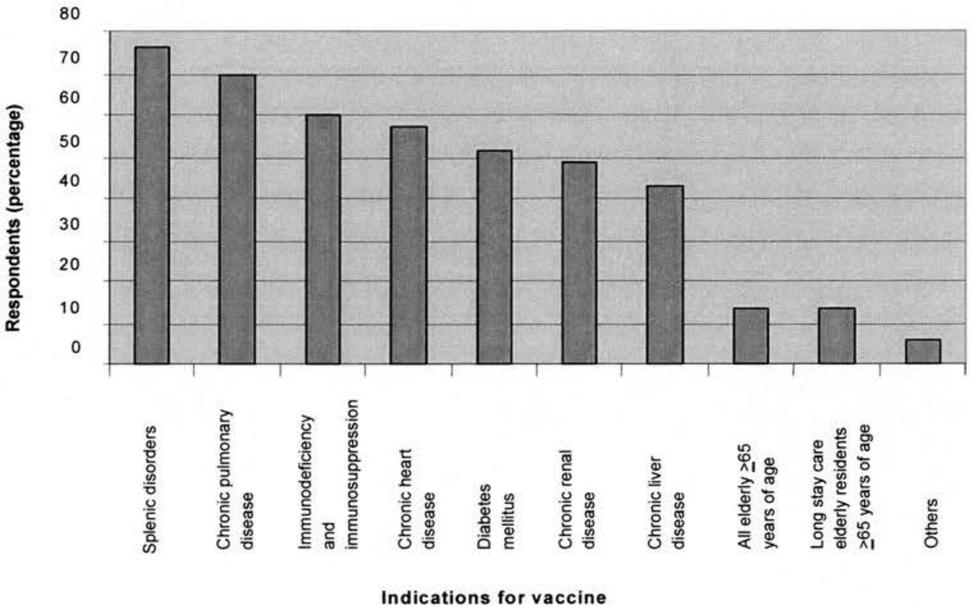
No vaccine distribution occurred until 1991. Rates of annual vaccine distribution increased from 0- to 63-doses/10^4 population during the period 1991-99 for the whole of Scotland (Figure 12). Only 1 to 7 doses/10^4 population were dispensed during the period 1992-1996. There was a substantial growth after 1996, from 30 in 1997 to 63 doses/10^4 population in 1999, following with the publication of the DoH recommendations for pneumococcal polysaccharide vaccination in 1996. Rates of vaccine distribution also rose from 1.9 in 1993 and to 68.1 in 1998 and to 50.1 in 1999 doses/10^4 population in the CMR practices (Figure 13).

Vaccine coverage reported in the questionnaire was 13% among patients recommended for the vaccine by the DoH. Variations in coverage of vaccine were noted in the eight risk categories, with lower coverage in patients with chronic renal disease and chronic pulmonary disease and higher coverage in the elderly (Table 24).

4.2.2.2. Views on vaccine indications

Views on vaccine indications among GPs are shown in Figure 14. Most GPs considered asplenic conditions (76%) and chronic pulmonary disease (70%) as the most important indications for vaccination. However, the elderly (including those living in long -term care facilities) were stated to be an indication for vaccination by only 13% of GPs.

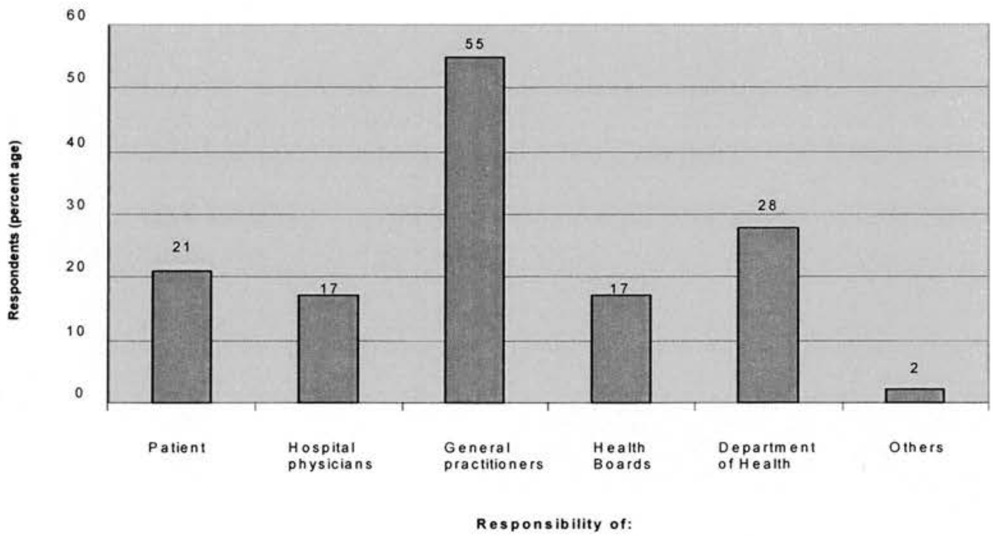
Figure 14. Views on pneumococcal polysaccharide vaccine indications



4.2.2.3. Vaccination responsibility and policies

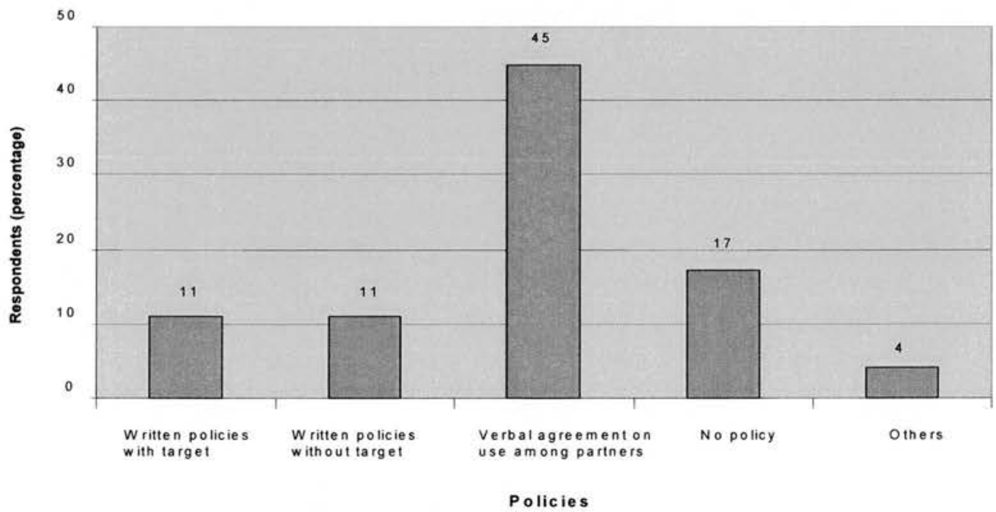
The groups with primary responsibility for vaccination as reported by questionnaire respondents are presented in Figure 15. A higher proportion of GPs (55%) believed that the responsibility for vaccination should lie with GPs. Vaccine use was not significantly related to views concerning the group with primary responsibility for vaccination (28/263 (11%) vs 24/151 (16%), $p = 0.126$).

Figure 15. Primary responsibility for pneumococcal polysaccharide vaccination



The existence of vaccination policies among GPs is shown in Figure 16. Only 11% of GPs reported that they had a pneumococcal vaccination policy with or without a set target. Many GPs (45%) reported that they had verbal agreement on its use among partners.

Figure 16. Policies for pneumococcal polysaccharide vaccination



4.2.2.4. Estimated high-risk patients and required immunisations

Table 25a shows the total numbers of high-risk patients in the 53 CMR practices. Using these data and vaccine prescription statistics, the cumulative vaccine coverage in 1993-99 was calculated only for the CMR practices. Coverage of PPV was 23.4% (5889/25120) among persons with high-risk conditions recommended by the DoH and 8.3% (5889/70615) among all high-risk conditions (including all elderly aged 65 years and above).

Table 25a. Number of patients with indications for pneumococcal polysaccharide vaccination in the CMR practices and estimated number of required vaccinations in Scotland

High-risk conditions*	Number of patients in the CMR practices**	Number of required pneumococcal polysaccharide vaccinations for the whole of Scotland
Chronic liver disease	265	
Chronic pulmonary disease	13,696	
Chronic renal disease	318	
Diabetes	3,991	418,646
Chronic heart disease	6,684	
Immunosuppression/immunodeficiency	41	
Asplenia	125	

Table 25b. Estimated vaccine coverage in the elderly in the CMR practices and the whole of Scotland

Number of required pneumococcal polysaccharide vaccinations for the elderly	CMR practices only	The whole of Scotland
Elderly 65 years of age and above	45,495	1,202,787
Elderly 75 years of age and above	20,150	760,948

* *DoH recommendations for pneumococcal polysaccharide vaccination include all listed high-risk conditions except the elderly*

** *Patients are based on person (patients with two high-risk conditions = 1374, three high-risk conditions = 78 and four high-risk conditions = 2)*

The estimated total numbers of high-risk patients (with and without the elderly) or required pneumococcal immunisations for the whole of Scotland was also projected based on the total of high-risk patients registered in the CMR practices (Table 25a/b).

4.2.2.5. Place of vaccination

The majority of pneumococcal vaccination (94.2%) took place in general practice. Very few patients (3.8%) had received pneumococcal vaccination at home. Only 2% of pneumococcal vaccination occurred in hospital care settings.

4.2.2.6. Socio-economic status in relation to vaccine coverage

The coverage of pneumococcal vaccination differed by deprivation status categories of residence of patients (Table 26). A statistically significant association between deprivation category and vaccination was noted ($p = 0.01$, χ^2 for trend = 6.5) but trend not easy to interpret.

Table 26. Level of pneumococcal polysaccharide vaccine coverage in relation to deprivation category

Deprivation Category*	Pneumococcal vaccine No	(%)	Yes	(%)	
1	15	(4.3)	4	(8)	19
2	43	(12.3)	7	(14)	50
3	90	(25.6)	22	(44)	112
4	132	(37.6)	13	(26)	145
5	24	(6.8)	2	(4)	26
6	38	(10.8)	2	(4)	40
7	9	(2.6)	-	(0)	9
P = 0.01, $\chi^2$for trend = 6.5)	351	(100)	50	(100)	401

*Carstairs deprivation index which is based at postcode sector of patients' area of residence.It is the most common type of deprivation indicator used in the Scottish Health Service. * 1 being the most affluent and 7 being the most deprived*

4.2.3. Survey 3: Characteristics of pneumococcal polysaccharide vaccination in nursing homes

Although influenza vaccine is recommended for all elderly aged 65 years and above and persons in long-term care facilities, PPV is not yet recommended for these vulnerable groups in the UK. There are limited data on coverage and policies of pneumococcal polysaccharide vaccination in UK nursing homes. The reasons for receipt and non-receipt of vaccine in the elderly home residents are poorly understood. This survey was conducted to determine PPV coverage, policies and the factors associated with use and receipt of vaccine in Scottish nursing homes.

Of the 550 nursing homes surveyed, 394 homes (72%) responded to the questionnaire. The mean size of home was 46 residents. The number of general practices looking after residents ranged from 1 to 24 practices, with a mean of 5 practices. The presence of systematic immunisation records, defined as completed documentation of immunisation history, was reported by 6% (23/394) of nursing homes.

There were no significant differences in median pneumococcal vaccination rates for the following covariates: areas of Scotland by Health Boards ($p=0.37$, Kruskal-Wallis test), the presence of systematic immunisation record ($p=0.55$), the number of GPs per home (<5 GPs=0% vs. >5 GPs=0%, $p=0.10$ respectively).

No significant association between the number of residents and the median vaccination rates was found for PPV (<30 residents vs 31-50 residents vs >51 residents, $P=0.71$, Kruskal-Wallis test). There was a significantly higher median coverage of PPV in nursing homes with a pneumococcal vaccine policy compared with those who did not have one (P=0.007).

4.2.3.1. Vaccine coverage

Of the 394 homes returning the questionnaire, information on vaccine coverage of pneumococcal vaccination was provided by only 142 homes. Thus, vaccine coverage was calculated based on the appropriate denominators (homes reporting data on vaccine coverage). Overall, vaccine coverage was 11% for PPV in the last five years among 13,700 residents. Less than 5% PPV coverage among residents was documented in 74% of nursing homes (Table 27).

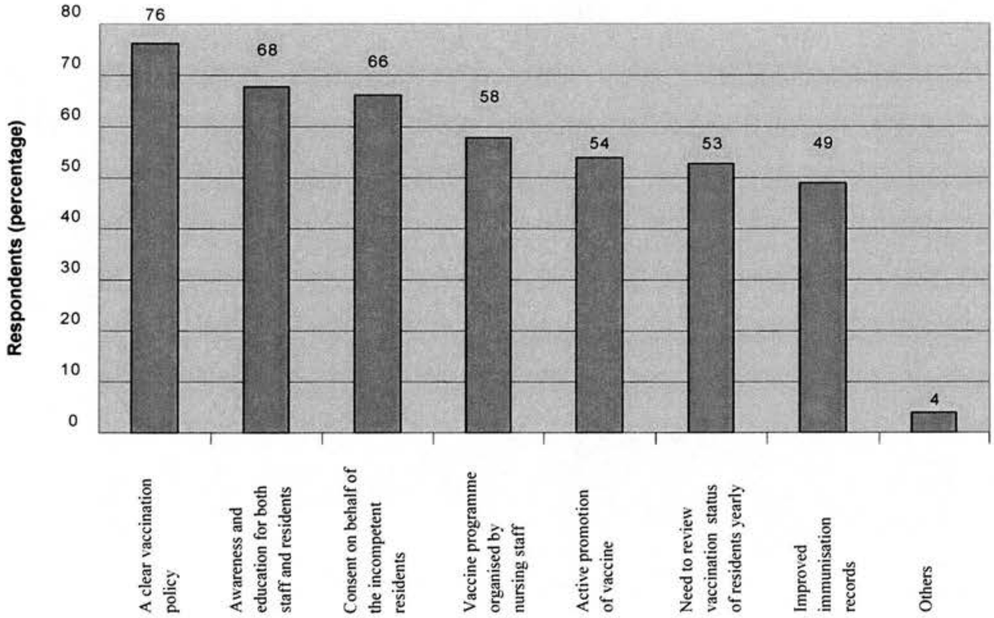
Table 27. Pneumococcal polysaccharide vaccine coverage among nursing homes, which provided information on vaccination

Percentage of residents received pneumococcal polysaccharide vaccine	Number (%) of nursing homes with vaccine coverage	
<5	105	(74)
5-9	11	(8)
10-19	8	(6)
20-49	6	(4)
≥50	12	(8)
Total	142	(100)

4.2.3.2. Strategies for improving vaccine coverage

The most frequently reported strategies for having improved coverage of PPV were a clear immunisation policy (76%), awareness and education of staff and residents (68%) and consent on behalf of mentally incompetent residents (66%) (Figure 17).

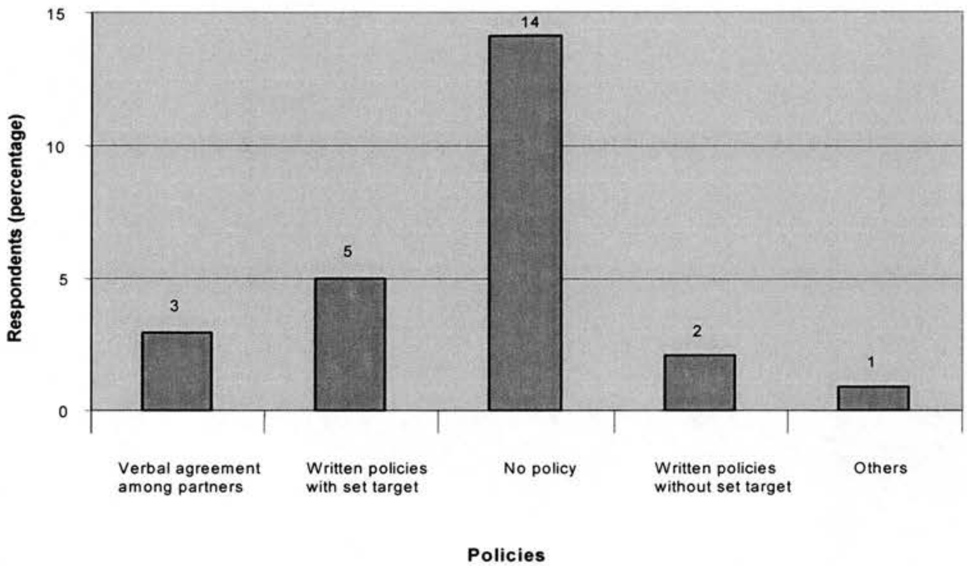
Figure 17. Factors considered important for improving pneumococcal polysaccharide vaccine in nursing homes



4.2.3.3. Vaccination policies

Of the 394 responding homes, 42 (10%) nursing homes had a vaccination policy for PPV in one form or another including verbal agreement (3%), written policies with set target (5%) and written policies without set target (2%) (Figure 18).

Figure 18. Policies on pneumococcal polysaccharide vaccination in nursing homes*

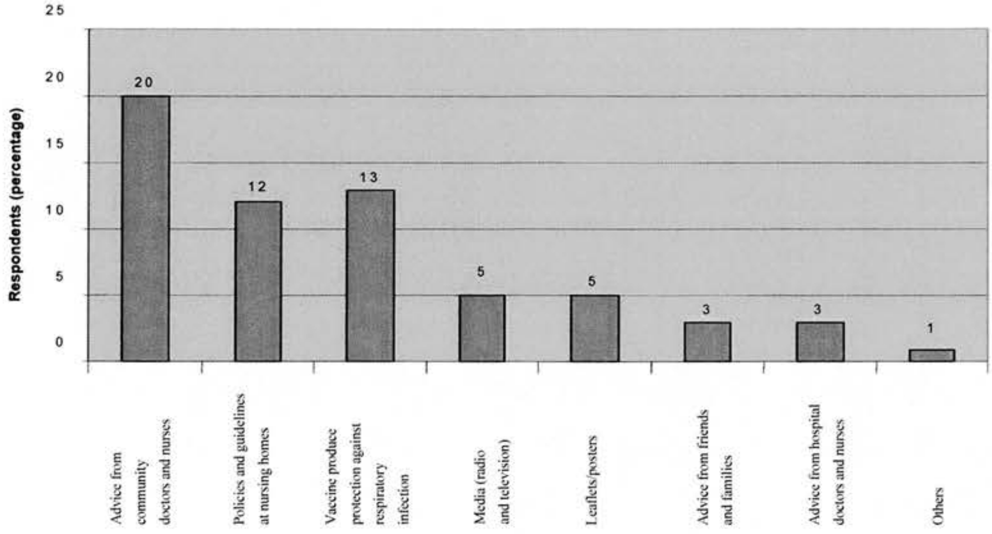


** Percentages do not add up to 100% because respondent rate for this question was 25%*

4.2.3.4. Main reasons for receipt and non-receipt of pneumococcal polysaccharide vaccine

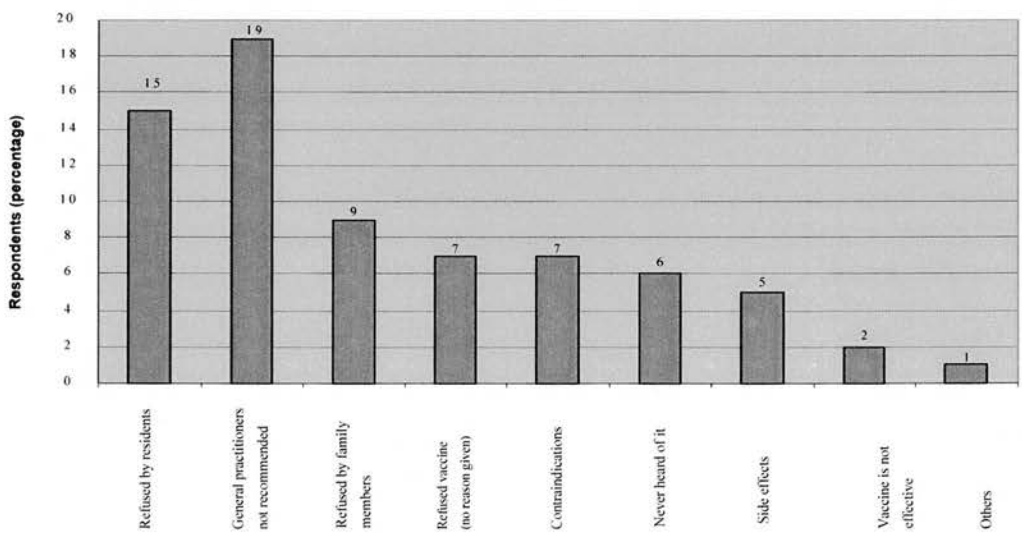
The most common reasons for receipt of PPV were advice from community doctors and nurses (20%), nursing home policies and guidelines (12%) and efficacy against respiratory infection (13%) (Figure 19).

Figure 19. Main reasons for receipt of pneumococcal polysaccharide vaccine



The main reasons for non-receipt of PPV were that it was not recommended by their GPs (19%) and refusals by residents (15%) (Figure 20).

Figure 20. Main reasons for non-receipt of pneumococcal polysaccharide vaccine in nursing homes



4.2.4. Survey 4: Vaccination in splenectomised patients

This survey identified the coverage of preventive measures in splenectomised patients in Scotland from 1988 to 1998. These include antibiotics, polysaccharide pneumococcal, meningococcal and conjugate Hib vaccines.

Of the 1648 patients who underwent splenectomy during the study period 1988-1998, 974 were alive in 2001. Of these alive patients, information on vaccination status was available for 708 (73%) of patients. There was a higher coverage of PPV (622/708, 88%) and Hib conjugate vaccine (468/664, 70%) than meningococcal polysaccharide vaccine (317/619, 51%) in these patients (Table 28).

Table 28. Vaccine and prophylactic antibiotic coverage among splenectomised patients

Vaccine or antibiotic prophylaxis	Timing of vaccination	Coverage Number	(%)
Pneumococcal vaccine only	All cases (pre- or post-operation) Two weeks prior to elective operation	622/708 153/541	(88) (28)
Hib vaccine only	All cases (pre- or post-operation) Two weeks prior to elective operation	468/664 83/435	(70) (19)
Meningococcal vaccine only	All cases (pre- or post-operation) Two weeks prior to elective operation	317/619 48/335	(51) (14)
Influenza vaccine only	All cases (pre- or post-operation) Season 1997-1998 Season 1998-1999 Season 1999-2000 Season 2000-2001	 16/21 24/27 82/89 329/342	 (76) (89) (92) (96)
Antibiotic prophylaxis only	Postsplenectomy	518/770	(67)
Pneumococcal and Hib vaccines	All cases (pre- or post-operation) Two weeks prior to elective operation	439/641 80/406	(68) (20)
Pneumococcal and meningococcal vaccines	All cases (pre- or post-operation) Two weeks prior to elective operation	305/602 44/313	(51) (14)
Hib and meningococcal vaccines	All cases (pre- or post-operation) Two weeks prior to elective operation	276/588 40/305	(47) (13)
Pneumococcal, meningococcal and Hib vaccines	All cases (pre- or post-operation) Two weeks prior to elective operation	269/576 38/291	(47) (13)
Pneumococcal and Hib vaccines and antibiotic prophylaxis*	**All cases (pre- and post-operation) for vaccines and post-operation for antibiotic prophylaxis**	**333/634**	**(52)**
Pneumococcal, meningococcal and Hib vaccines and antibiotic prophylaxis	All cases (pre- and post-operation) for vaccines and post-operation for antibiotic prophylaxis	201/571	(35)

* *Main Department of Health (DoH)[458] and British Committee for Standards in Haematology (BCSH)[613] recommendations include* ***pneumococcal and Hib vaccine and antibiotic prophylaxis***

All three vaccines were received by (269/576, 47%) of the patients. Vaccination status prior to elective splenectomy was recorded for 541 (56%) of the patients. Coverage of PPV (153/541, 28%) was higher than that of Hib (83/435, 19%) or meningococcal polysaccharide vaccine (48/335, 14%) for elective splenectomy. All three vaccines were received by 13% (38/291) of the patients.

There was an increasing trend in coverage of influenza vaccine between 1997 and 2000, from 76% in 1997-1998 season to 96% in 2000-2001 season. Of the 770 (79%) patients in whom antibiotic status was recorded, 518 (67%) received antibiotic prophylaxis. Coverage was 35% (201/571) for all three vaccines and antibiotic prophylaxis and 52% (333/634) for pneumococcal and Hib and antibiotic prophylaxis.

4.2.4.1. Preventive measures in relation to deprivation status category of residence of patients

There were no significant trends in the deprivation status category values for coverage of vaccine with (p=0.12) or without antibiotic prophylaxis for combination of pneumococcal and Hib vaccine (p=0.14). Similar findings were recorded for combination of pneumococcal, meningococcal and Hib vaccine with (p=0.07) or without antibiotic prophylaxis (p=0.08). Nor did influenza vaccine coverage relate to the deprivation index (Fisher's exact test, p= 0.46).

4.3. To estimate coverage of pneumococcal vaccine for serotypes associated with disease and antibiotic non-susceptibility

4.3.1. Invasive serotypes distribution

Serotype information was available for 1531 isolates. 1426 (93.1%) had their serotype recorded between 1993-99, following the establishment of the SMPRL in 1992/93. Of the invasive isolates with serotypes information, 14.2% were from those under two years of age, 16.1% from aged five and less, 32.7% from age group 5-64 and 37.4% from aged 65 and above. Antibiotic susceptibility was tested on 1248/1531 (81.5%) of isolates for penicillin and on 1125/1531 (73.5%) of isolates for erythromycin.

The distribution among the 15 HBs in Scotland of isolates whose serotypes/groups were determined was as follows: Greater Glasgow, 428; Lothian, 400; Lanarkshire, 235; Grampian, 120; Ayrshire and Arran, 88; Argyll and Clyde, 60; Forth Valley, 53; Tayside, 51; Highland, 44; Borders, 20; Fife, 13; Dumfries and Galloway, 12; Western Isles, 4; Orkney and Shetland, 0; and unknown area, 3.

4.3.1.1. IPD related serotypes

The most common serotypes were 14, 6, 19, 23, 9, 18, 7, 4, 3, 1 and 8 but varied in their orders among different age groups (Table 29). These serotypes were responsible for over 80% of all invasive pneumococcal isolates in all ages. Overall, type 14 was the most prevalent serotype, accounting for 10-32% of invasive isolates in all age groups except for the 5-64 years age group. Serotype 1 was the most prevalent in age group 5-64 years and caused 13% of invasive isolates.

The prevalence of most common serotypes varied year to year of the period 1993-99 (Table 30). Notably, there has been an increase in the proportion of serotype 14 over the study period.

Table 29. Most prevalent (11) pneumococcal serotypes by age group

Serotypes	<2 years Number of isolates (%)	Serotypes	≤ 5years Number of isolates (%)	Serotypes	5-64 years Number of isolates (%)	Serotypes	≥ 65 years Number of isolates (%)	Serotypes	All ages Number of isolates (%)
14	69 (31.8)	**14**	72 (29.3)	**1**	66 (13.2)	**14**	83 (14.5)	**14**	254 (16.6)
6	38 (17.5)	**6**	40 (16.3)	**9**	55 (11.0)	**19**	61 (10.6)	**9**	144 (9.4)
19	22 (10.1)	**23**	24 (9.8)	**14**	52 (10.4)	**3**	56 (9.8)	**19**	140 (9.4)
23	22 (10.1)	**19**	23 (9.3)	**7**	36 (7.2)	**9**	53 (9.2)	**6**	133 (8.7)
9	14 (6.5)	**18**	18 (7.3)	**4**	36 (7.2)	**23**	47 (8.2)	**23**	126 (8.2)
18	10 (4.6)	**9**	16 (6.5)	**3**	30 (6.0)	**4**	41 (7.2)	**1**	114 (7.4)
7	8 (3.7)	**7**	10 (4.1)	**8**	29 (5.8)	**6**	41 (7.2)	**3**	104 (6.8)
4	7 (3.2)	**1**	9 (3.7)	**6**	29 (5.8)	**1**	35 (6.1)	**4**	94 (6.1)
3	6 (2.8)	**4**	8 (3.3)	**19**	28 (5.6)	**8**	26 (4.5)	**7**	70 (4.6)
1	5 (2.3)	**3**	6 (2.4)	**23**	31 (6.2)	**22**	19 (3.3)	**8**	64 (4.2)
8	2 (0.9)	**8**	2 (0.8)	**22**	18 (3.6)	**7**	18 (3.1)	**18**	40 (2.6)
Total+	203 (93.5)		228 (92.7)		410 (82)		480 (83.8)		1283 (83.8)
Total*	217 (100)		246 (100)		500 (100)		573 (100)		1531 (100)

** = Overall total, + = total for top 11 serotypes*

Table 30. Most prevalent (11) serotypes: annual variation, 1993-99

Serotypes	Number of isolates							Total
	1993	1994	1995	1996	1997	1998	1999	
1	15	22	16	23	11	11	7	105
3	11	16	15	14	20	9	6	91
4	13	9	20	12	10	10	11	85
6	22	17	17	24	13	18	17	128
7	8	12	14	4	13	9	3	63
8	10	12	6	6	11	7	8	60
9	19	11	19	21	12	30	24	136
14	21	31	26	35	29	52	50	244
18	4	10	5	3	3	8	1	34
19	21	20	18	15	15	23	20	132
23	14	23	13	17	14	13	26	120
Others	30	46	32	32	30	27	31	228
Total§	158	183	169	174	151	190	173	1198
Total*	188	229	201	206	181	217	204	1426

** = All total serotypes in each year, § = A total of top 11 serotypes in each year*

4.3.1.2. Penicillin/erythromycin non-susceptibility related serotypes

The distribution of penicillin and erythromycin susceptible and non-susceptible serotypes is shown in Table 31. Serotype 14 was reported in two high-level penicillin resistant blood isolates. It also accounted for 20.6% of all penicillin non-susceptible isolates and 75% of all erythromycin non-susceptible isolates. Serotypes 6, 9, 14, 19 and 23 were responsible for 94.3% penicillin non-susceptibility and for 99.1% erythromycin non-susceptibility.

Table 31. Penicillin and erythromycin non-susceptible invasive pneumococcal serotypes

Penicillin susceptibility Number						Erythromycin susceptibility Number					
MIC	ST	CSF	Blood	Others	Total	MIC	ST	CSF	Blood	Others	Total
	1	3	90	4	97		**1**	2	74	5	81
	2	-	6	-	6		**2**	-	6	-	6
	3	7	67	6	80		**3**	8	56	5	69
	4	7	69	3	79		**4**	6	53	3	62
	5	-	1	-	1		**5**	-	2	-	2
	6	17	66	3	86		**6**	13	63	4	80
	7	5	51	1	57		**7**	5	43	1	49
	8	8	45	1	54		**8**	7	38	1	46
S	**9**	8	83	1	92	**S**	**9**	7	88	81	176
	10	-	9	1	10		**10**	-	8	-	8
	11	3	23	1	27		**11**	2	20	-	22
	12	5	24	-	29		**12**	4	21	-	25
	13	-	2	-	2		**13**	-	1	-	1
	14	25	151	9	185		**14**	5	83	8	96
	15	1	14	1	16		**15**	1	12	-	13
	16	1	5	-	6		**16**	1	4	-	5
	17	1	3	-	4		**17**	1	3	-	4
	18	10	23	-	33		**18**	7	18	-	25
	19	11	89	3	103		**19**	9	79	5	93
	20	-	15	-	15		**20**	-	14	-	14
	21	-	1	-	1		**21**	-	1	-	1
	22	5	28	-	33		**22**	5	22	-	27
	23	14	65	5	84		**23**	10	62	6	78
	24	2	3	-	5		**24**	1	3	-	4
	27	-	-	1	1		**27**	-	-	1	1
	29	-	4	-	4		**29**	-	4	-	4
	31	1	6	-	7		**31**	1	5	-	6
	38	1	9	-	10		**38**	1	6	-	7
	34	-	3	1	4		**34**	-	3	1	4
	35	-	3	-	3		**35**	-	2	-	2
	38	-	5	-	5		**38**	-	4	-	4
	41	-	1	-	1		**41**	-	1	-	1
	42	-	1	-	1		**42**	-	1	-	1
Total		135	965	41	1141			96	800	121	1017
	1	-	-	1	1		**1**	-	-	-	-
	3	1	1	1	3		**3**	-	-	-	-
	4	-	-	-	-		**4**	-	1	-	1
	5	-	1	-	1		**5**	-	-	-	-
	6	-	19	3	22		**6**	-	10	2	12
I	**8**	-	1	-	1	**R**	**8**	-	-	-	-
	9	1	23	9	33		**9**	-	3	2	5
	14	-	18	2	20		**14**	16	63	2	81
	15	-	1	-	1		**15**	-	-	-	-
	19	-	8	2	10		**19**	1	4	-	5
	23	-	9	3	12		**23**	-	3	1	4
	29		1	-	1		**29**	-	-	-	-
Total		2	82	21	105						
R	**14**	-	2	-	2						
Total		-	2	-	2	**Total**		17	84	7	108

S = sensitive isolates, I = intermediate isolates, R = resistant isolates= non-susceptible = intermediate and resistant, ST = serotypes
MIC = minimum inhibitory concentration

4.3.2. Potential coverage of vaccine for invasive isolates

4.3.2.1. By age group

The 14- and 23-valent PPV covered more than 88.4% and 96.4% of invasive isolates, respectively, in all ages. Serotypes in the 7 to 11-valent PCV caused between 82% and 93% of invasive disease in age group 5 years and less but a lower percentage in the older age groups (Table 32). The marked annual variation in coverage of PCV was noted in different age groups in 1993-99 (Table 33).

Table 32. Vaccine coverage of pneumococcal serotypes in different age groups

Vaccine	Number of vaccine related isolates (%)									
	<2 years		≤5 years		5-64years		≥65years		All ages	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
23§	N/A	N/A	244	(99.2)	475	(95)	550	(96)	1476	(96.4)
14†	N/A	N/A	232	(94.3)	427	(85.4)	481	(83.9)	1354	(88.4)
11‡	201	(92.6)	226	(91.9)	379	(75.8)	440	(76.8)	1221	(79.8)
9¶	187	(86.2)	210	(85.4)	313	(62.6)	366	(63.9)	1047	(68.4)
7±	182	(83.9)	201	(81.7)	247	(49.4)	331	(57.8)	931	(60.8)
Total	217	(100)	246	(100)	500	(100)	573	(100)	1531	(100)

§ 23-valent polysaccharide vaccine, † 14-valent vaccine (not in use), ‡ 11-valent conjugate vaccine, ¶ 9-valent conjugate vaccine, ±7-valent conjugate vaccine
N/A = not applicable (polysaccharide vaccines are not recommend for children under two years of age)

7-valent vaccine serotypes:	4, 6B, 9V, 14, 18C, 19F, 23F
9-valent vaccine serotypes:	1, 4, 5, 6B, 9V, 14, 18C, 19F and 23F
11-valent vaccine serotypes:	1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F
14-valent vaccine serotypes (not in use):	1, 2, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18C, 19F, 23F and 25
23-valent vaccine serotypes:	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F

Table 33. Coverage of pneumococcal vaccines for <2 years old, $\leq$ 5 years old, $\geq$ 65 years old and all ages by year 1993-99

	<2 years Number of vaccine related serotypes (%)				$\leq$ 5 years Number of vaccine related serotypes (%)				$\geq$ 65 years Number of vaccine related serotypes (%)				All ages Number of vaccine related serotypes (%)			
Year	**23§**	**11‡**	**9¶**	**7±**	**23§**	**11‡**	**9¶**	**7±**	**23§**	**11‡**	**9¶**	**7±**	**23§**	**11‡**	**9¶**	**7±**
1993	26(100)	24(92.3)	23(88.5)	22(84.6)	27(100)	25(92.6)	25(92.6)	24(88.9)	47(90.4)	42(80.8)	39(75)	35(67.3)	180(95.7)	148(78.7)	129(68.6)	114(60.0)
95 % CI	(87,100)	(75,99)	(70,98)	(65,96)	(87,100)	(76,99)	(76,99)	(71,98)	(79,97)	(67,90)	(61,86)	(53,80)	(92,98)	(72,84)	(61,75)	(53,68)
1994	35(97.2)	34(94.4)	32(88.9)	29(80.6)	42(97.7)	41(95.4)	38(88.4)	33(76.7)	73(94.8)	44(57.1)	36(46.8)	32(41.6)	220(96.1)	171(74.7)	143(62.4)	121(52.8)
95 % CI	(85,100)	(81,99)	(74,97)	(64,92)	(88,100)	(84,99)	(75,96)	(61,88)	(87,99)	(45,68)	(35,58)	(30,53)	(93,98)	(69,80)	(56,69)	(46,60)
1995	22(100)	17(77.3)	14(63.6)	13(59.1)	26(100)	21(80.8)	18(69.2)	17(65.4)	77(96.3)	70(87.5)	55(68.7)	48(60)	193(96.0)	163(81.1)	134(66.7)	118(58.7)
95 % CI	(85,100)	(55,92)	(41, 83)	(36,79)	(87,100)	(61,93)	(48,86)	(44,83)	(89,99)	(78,94)	(57,79)	(48,71)	(92,98)	(75,86)	(60,73)	(52,66)
1996	29(100)	29(100)	28(96.6)	28(96.6)	33(100)	31(93.9)	30(90.9)	30(90.9)	80(95.2)	68(80.9)	58(69)	48(57.1)	199(96.6)	168(81.6)	150(72.8)	127(61.6)
95 % CI	(88,100)	(88,100)	(82,100)	(82,100)	(89,100)	(80,99)	(76,98)	(76,98)	(88,99)	(71,89)	(58,79)	(46,68)	(93,99)	(76,87)	(66,79)	(55,68)
1997	23(100)	22(95.7)	22(95.7)	22(95.7)	29(100)	27(93.1)	27(93.1)	25(86.2)	84(98.8)	66(77.7)	46(54.1)	44(51.8)	175(96.7)	142(78.5)	109(60.2)	96(53.0)
95 % CI	(85,100)	(78,100)	(78,100)	(78,100)	(88,100)	(77,99)	(77,99)	(68,96)	(94,100)	(67,86)	(43,65)	(41,63)	(93,99)	(72,84)	(53,67)	(45,60)
1998	38(97.4)	36(92.3)	35(89.7)	35(89.7)	41(97.6)	39(92.9)	38(90.5)	38(90.5)	74(97.4)	62(81.6)	55(72.4)	51(67.1)	209(96.3)	179(82.5)	165(76.0)	154(70.9)
95 % CI	(87,100)	(79,98)	(76,97)	(76,97)	(87,100)	(81,99)	(77,97)	(77,97)	(91,100)	(71,90)	(61,82)	(55,77)	(93,98)	(77,87)	(70,82)	(65,77)
1999	29(100)	26(89.7)	23(79.3)	23(79.3)	31(100)	27(87.1)	23(74.2)	23(74.2)	73(97.3)	56(74.7)	53(70.7)	52(69.3)	201(98.5)	165(80.9)	156(76.5)	149(73.0)
95 % CI	(88,100)	(73,98)	(60,92)	(60,92)	(89,100)	(70,96)	(55,88)	(55,88)	(91,100)	(63,84)	(59,81)	(58,79)	(96,100)	(75,86)	(70,82)	(66,79)

CI = Confidence interval

§ 23-valent polysaccharide vaccine, ‡ 11-valent conjugate vaccine, ¶ 9-valent conjugate vaccine, ±7-valent conjugate vaccine

4.3.2.2. By antibiotic susceptibility

The 14- and 23-valent PPV serotypes covered over 86% of penicillin and erythromycin susceptible isolates respectively (Table 34). Both polysaccharide vaccines covered over 98% penicillin and erythromycin non-susceptible isolates. The 7, 9- and 11-valent PCVs included 57 to 79% of penicillin and erythromycin susceptible isolates. Above 94% coverage with all conjugate vaccines was noted for penicillin and erythromycin non-susceptible isolates.

Table 34. Penicillin and erythromycin susceptible and non-susceptible pneumococcal serotypes covered by the vaccines

Vaccine	Penicillin								Erythromycin					
	Sensitive Number (%)		Intermediate Number (%)		Resistant Number (%)		Total Number (%)		Sensitive Number (%)		Resistant Number (%)		Total Number (%)	
23§	1100	(97.3)	104	(99.0)	2	(100)	1206	(96.6)	910	(96.3)	108	(100)	1018	(96.7)
14†	985	(86.3)	103	(98.1)	2	(100)	1090	(87.3)	813	(86.0)	108	(100)	921	(87.5)
11‡	897	(78.6)	102	(97.1)	2	(100)	1001	(80.2)	738	(78.1)	108	(100)	846	(80.3)
9¶	760	(66.6)	99	(94.3)	2	(100)	861	(69)	620	(65.6)	108	(100)	728	(69.1)
7±	662	(58.0)	97	(97.4)	2	(100)	761	(61)	537	(56.8)	108	(100)	645	(61.3)

Non-susceptible = intermediate and resistant

§ 23-valent polysaccharide vaccine, † 14-valent vaccine (not in use), ‡ 11-valent conjugate vaccine,
¶ 9-valent conjugate vaccine, ±7-valent conjugate vaccine

4.3.3. Non-invasive serotype distribution

There were 4491 non-invasive isolates in 1988-99, comprising 3988 (88.8%), 79 (1.8%) and 424 (9.4%) from sputum, nasopharynx and other superficial sites respectively. Serological information was available for 1011 (22.5%) isolates, in which 524 had specific serotype information and 833 had serotype information (Table 35). Of these serotyped isolates, 654 (64.7%) isolates were from sputum, 79 (7.8%) from the nasopharynx and 278 (27.5%) from other non-invasive sites. Susceptibility to penicillin and erythromycin was tested in 60.4% (611/1011) and 50% (505/1011) of all isolates which were serotyped. The prevalence of non-susceptible isolates was 373/611 (61%) for penicillin in 1992-99 and of 70/505 (14%) for erythromycin in 1994-99 for the isolates for which there was serotype information.

Table 35. Distribution of non-invasive pneumococcal serotypes

Serogroups			Serotypes			Serogroups/types		
Groups	*Number*	*Percent (%)*	*Groups*	*Number*	*Percent (%)*	*Groups*	*Number*	*Percent (%)*
23	224	26.9	**23F**	77	14.7	**23**	224	22.2
			23A	12	2.3			
9	166	19.9	**19F**	57	10.9	**9**	166	16.4
			19A	18	3.4			
6	150	18	**14**	69	13.2	**6**	150	14.8
19	138	16.6	**6A**	32	6.1	**19**	138	13.6
			6B	30	5.7			
15	36	4.3	**9V**	36	6.9	**14**	69	6.8
			9N	13	2.5			
11	35	4.2	**15B**	16	3.1	**3**	54	5.3
			15C	6	1.1			
			15A	3	0.6			
			15F	3	0.6			
33	18	2.2	**11A**	33	6.3	**15**	36	3.6
			11C	1	0.2			
7	15	1.8	**33F**	16	3.1	**11**	35	3.5
10	15	1.8	**10A**	14	2.7	**33**	18	1.8
18	13	1.6	**8**	13	2.5	**7**	15	1.5
17	6	0.7	**1**	12	2.3	**10**	15	1.5
12	5	0.6	**18C**	12	2.3	**8**	13	1.3
16	5	0.6	**7F**	9	1.7	**18**	13	1.3
			7C	1	0.2			
22	3	0.4	**35**	7	1.3	**1**	12	1.2
24	3	0.4	**17F**	6	1.1	**35**	9	0.9
41	1	0.1	**31**	5	1	**17**	6	0.6
			12F	3	0.6	**12**	5	0.5
			27	3	0.6	**16**	5	0.5
			29	3	0.6	**31**	5	0.5
			4	2	0.4	**22**	3	0.3
			20	2	0.4	**24**	3	0.3
			22A	2	0.4	**27**	3	0.3
			34	2	0.4	**29**	3	0.3
			42	2	0.4	**4**	2	0.2
			5	1	0.2	**20**	2	0.2
			16F	1	0.2	**34**	2	0.2
			24F	1	0.2	**42**	2	0.2
			37	1	0.2	**5**	1	0.1
						37	1	0.1
						41	1	0.1
Total	833	100	**Total**	524	100	**Total**	1011	100

4.3.3.1. Non-invasive pneumococcal disease related serotypes

The eight most prevalent pneumococcal serotypes (in descending rank order) were 23, 9, 6, 19, 14, 3 15, and 11. These eight serotypes were responsible for over 86.3% of non-invasive disease regardless of specimen type (Table 35). The frequency of serotypes associated with NIPD, by age group, is shown in Table 36. Serotypes 23, 9, 6, 19 and 14 accounted for the majority of penicillin and erythromycin non-susceptibility (Table 37).

Table 36. Serotype distribution of non-invasive pneumococcal isolates by age group, 1988-99

< 2 years			≤ 5 years			5-64 years			≥ 65 years		
ST	No.	%	ST	No.	%	*ST*	No.	%	*ST*	No.	%
23	52	(28.0)	**23**	55	(26.3)	**23**	67	(20.8)	**23**	82	(21.9)
6	45	(24.2)	**6**	49	(23.4)	**6**	47	(14.6)	**9**	67	(17.9)
19	30	(16.1)	**19**	32	(15.3)	**9**	46	(14.3)	**19**	52	(13.9)
9	22	(11.8)	**9**	26	(12.4)	**19**	41	(12.7)	**6**	42	(11.2)
3	12	(6.5)	**3**	15	(7.2)	**3**	18	(5.6)	**14**	32	(8.5)
14	11	(5.9)	**14**	14	(6.7)	**11**	14	(4.3)	**15**	19	(5.1)
11	4	(2.2)	**11**	6	(2.9)	**14**	13	(4.0)	**3**	17	(4.5)
10	2	(1.1)	**15**	3	(1.4)	**15**	13	(4.0)	**33**	12	(3.2)
15	2	(1.1)	**10**	2	(1.0)	**18**	10	(3.1)	**11**	10	(2.7)
24	2	(1.1)	**1**	1	(0.5)	**8**	8	(2.5)	**7**	8	(2.1)
7	1	(0.5)	**4**	1	(0.5)	**10**	5	(1.6)	**10**	7	(1.9)
1	1	(0.5)	**7**	1	(0.5)	**7**	5	(1.6)	**8**	4	(1.1)
4	1	(0.5)	**17**	1	(0.5)	**1**	5	(1.6)	**17**	4	(1.1)
20	1	(0.5)	**20**	1	(0.5)	**12**	4	(1.2)	**35**	4	(1.1)
			24	2	(1.0)	**4**	1	(0.3)	**18**	3	(0.8)
						16	4	(1.2)	**29**	3	(0.8)
						33	4	(1.2)	**27**	2	(0.5)
						35	4	(1.2)	**31**	2	(0.5)
						17	2	(0.6)	**12**	1	(0.3)
						22	2	(0.6)	**16**	1	(0.3)
						31	2	(0.6)	**22**	1	(0.3)
						34	2	(0.6)	**24**	1	(0.3)
						5	1	(0.3)	**37**	1	(0.3)
						20	1	(0.3)			
						27	1	(0.3)			
						41	1	(0.3)			
						42	1	(0.3)			
Total	**186**	**100.0**		**209**	**100.0**		**322**	**(100.0)**		**375**	**100.0**

ST = serotype

Table 37. Penicillin and erythromycin susceptible and non-susceptible pneumococcal serotypes associated with non-invasive isolates

	Number (%) of isolates						
	Penicillin				**Erythromycin**		
Serotypes	Sensitive	Intermediate	Resistant	Total	Sensitive	Resistant	Total
23	72	78	5	155	110	24	134
9	14	115	4	133	113	5	118
6	24	61	0	85	53	19	72
19	35	45	0	80	55	8	63
14	12	46	1	59	43	11	54
Others*	81	18	0	99	61	3	64
Total §	157(66)	345(95)	10(100)	512(83.8)	374(86)	67(95.7)	441(87.3)
Total §§	238(100)	363(100)	10(100)	611(100)	435(100)	70(100)	505(100)

Non-susceptible isolates = intermediate and resistant, § Total isolates for serotypes (23, 9, 6, 19, 14), §§ Overall total isolates

*Others (sensitive = serotypes 11, 15, 1,7, 10, 31, 33,16, 4, 5, 22, 24, 29, 34, 35, 42) (intermediate = serotypes 8, 15, 7, 29, 1, 4, 18, 35) in descending order for penicillin

*Others (sensitive = serotypes 8, 15, 1, 7, 29, 31, 16, 4, 5, 18, 22,24, 33, 34,35, 42) (resistant = serotypes 4, 11, 15) in descending order for erythromycin

4.3.4. Potential vaccine coverage for non-invasive isolates

4.3.4.1. By age groups

The coverage of 14- and 23-valent PPV and 7- to 11-valent PCV varied for sputum, nasopharynx and other non-invasive sites in different age groups (Table 38). The 14- and 23-valent vaccine serotypes would cover over 91% of these non-invasive isolates in age group less than 2 years, over 88% in age group 5 years and less, 75-96% in age group 65 years and above and 82-99% in all ages. The 7, 9, and 11-valent conjugate vaccine in these age groups covers for 80-100%, 76-100%, 25-82% and 70-88% of non-invasive isolates respectively.

Overall, coverage of 7- to 11-valent conjugate vaccine serotypes for total non-invasive isolates was between 85% and 94% for age groups less than 2 years and 5 years and less but their coverage reduced to 74-84% in age groups 65 years and above and all ages. Overall, serotypes in the 14- and 23-valent polysaccharide vaccine caused 82-94% and 96-99% of total non-invasive disease, respectively in all age groups.

Table 38. Pneumococcal vaccine coverage for serotypes tested from non-invasive specimens by age groups

		Specimen type Number (%) of vaccine related serotypes							
Age group	Vaccine type	Sputum		Nasopharynx		Others		Total	
<2 years	23-valent§	10	(100)	44	(97.8)	130	(99.2)	184	(98.9)
	14-valent†	10	(100)	41	(91.1)	124	(94.7)	175	(94.1)
	11-valent‡	10	(100)	41	(91.1)	124	(94.7)	175	(94.1)
	9-valent¶	10	(100)	36	(80.0)	116	(88.5)	162	(87.1)
	7-valent±	10	(100)	36	(80.0)	115	(87.8)	161	(86.7)
	Total	10	(100)	45	(100)	131	(100)	186	(100)
≤5 years	23-valent	11	(100)	51	(98.1)	145	(99.3)	207	(99.0)
	14-valent	11	(100)	46	(88.5)	137	(93.8)	194	(92.8)
	11-valent	11	(100)	46	(88.5)	137	(93.8)	194	(92.8)
	9-valent	11	(100)	40	(76.9)	127	(87.0)	178	(85.2)
	7-valent	11	(100)	40	(76.9)	126	(86.3)	177	(84.7)
	Total	11	(100)	52	(100)	146	(100)	209	(100)
≥65 years	23-valent	327	(96.7)	3	(75)	31	(93.9)	361	(96.3)
	14-valent	279	(82.5)	3	(75)	26	(78.8)	308	(82.1)
	11-valent	276	(81.7)	1	(25)	26	(78.8)	303	(80.8)
	9-valent	255	(75.4)	1	(25)	22	(66.7)	278	(74.1)
	7-valent	255	(75.4)	1	(25)	22	(66.7)	278	(74.1)
	Total	338	(100)	4	(100)	33	(100)	375	(100)
All ages	23-valent	625	(95.6)	76	(96.2)	276	(99.3)	977	(96.6)
	14-valent	539	(82.4)	69	(87.3)	253	(91.0)	861	(85.2)
	11-valent	531	(81.2)	67	(84.8)	246	(88.5)	844	(83.5)
	9-valent	495	(75.7)	57	(72.2)	223	(80.2)	775	(76.7)
	7-valent	491	(75.7)	55	(69.6)	216	(77.7)	762	(75.4)
	Total	654	(100)	79	(100)	278	(100)	1011	(100)

§ 23-valent polysaccharide vaccine, † 14-valent vaccine (not in use), ‡ 11-valent conjugate vaccine, ¶ 9-valent conjugate vaccine, ±7-valent conjugate vaccine

4.3.4.2. By antibiotic susceptibility

The coverage of 7, 9, and 11-valent conjugate ranged from 74% to 94% of non-invasive isolates. The 23-valent PPV and all PCVs covered 94% and above of penicillin and erythromycin non-susceptible both invasive and non-invasive isolates (Table 39).

Table 39. Coverage of pneumococcal vaccines for penicillin and erythromycin susceptible and non-susceptible isolates

	Penicillin Number (%) of vaccine related serotypes								**Erythromycin** Number (%) of vaccine related serotypes					
Vaccine	Sensitive		Intermediate		Resistant		Total		Sensitive		Resistant		Total	
23§	228	(95.8)	360	(99.2)	10	(100)	598	(97.9)	423	(97.2)	70	(100)	493	(97.6)
11‡	194	(81.5)	353	(97.2)	10	(100)	557	(91.2)	405	(93.1)	68	(97.1)	473	(93.7)
9¶	166	(69.7)	348	(95.9)	10	(100)	524	(85.8)	382	(87.8)	68	(97.1)	450	(89.1)
7±	158	(66.4)	347	(95.6)	10	(100)	515	(84.3)	376	(86.4)	68	(97.1)	444	(87.9)
Overall	238	(100)	363	(100)	10	(100)	611	(100)	435	(100)	70	(100)	505	(100)

Non-susceptible = intermediate and resistant
§ 23-valent polysaccharide vaccine, ‡ 11-valent conjugate vaccine, ¶ 9-valent conjugate vaccine,
± 7 valent conjugate vaccine

5. DISCUSSION

5.1. Limitations of study methods and data

The present study provides data on the burden of IPD, the use of PPV and some of the limitations to the use of PPV in Scotland. The data presented in the study may be subject to the following potential biases and limitations. These should be borne in mind in interpretation of these data.

5.1.1. Laboratory data

5.1.1.1. Reporting

Laboratory reports on pneumococcal disease are based on passive surveillance; the voluntary reporting of cases from diagnostic laboratories. Therefore, it is likely that not all cases of IPD are reported to SCIEH and SMPRL, underestimating the true number of cases and thus underestimating the true incidence of disease. In addition, estimates of disease incidence were based on isolates from sterile body sites only, thus, these data do not reflect the true overall burden of pneumococcal disease in Scotland.

Nevertheless, an audit carried out by SCIEH and SMPRL showed over 90% completeness for referred pneumococci and reports of IPD in Scotland over the period 1994-99 (unpublished data, P Christie). In addition, the study results are supported by data from enhanced pneumococcal surveillance in Oxford between 1995 and 1999,[77] which reported similar data on age-specific incidence of IPD. To ensure the accuracy of study data, duplicate records for the same patient existing in SCIEH and SMPRL datasets were removed to avoid accounting more than once for the same patient. In addition, a consultant epidemiologist was responsible for reviewing these laboratory data every week for the completeness of case ascertainment and reliability. These measures strengthen the validity of the study results.

The observed increase in the number of cases of pneumococcal disease after 1992 is probably due to the establishment of SMPRL, which encourages all diagnostic laboratories to send isolates from body fluids of patients with suspected pneumococcal disease. Moreover, improved awareness of the disease among clinicians and the public may also play a role in the increase in incidence of IPD in the recent years.

5.1.1.2. Number of participating laboratories

The number of laboratories reporting cases of pneumococcal disease to SCIEH or SMPRL increased from 29 to 33 between 1988 and 1999. The four additional laboratories began reporting after 1994. It is possible that this affected the study results. The total number of cases of IPD ranged from 296 to 536 in 1988-93 and from 552 to 646 in 1994-99. However, a clear increase in the incidence of IPD was observed prior to 1994 (Figure 1a), suggesting that the participation of four additional laboratories is unlikely to explain most of the observed increase in the incidence of IPD.

Between 1983 and 1999, the number of laboratories reporting to SCIEH has increased for the five pathogens causing invasive bacterial disease; from 29 to 33 for pneumococci and meningococci, from 25 to 28 for GBS and *H. influenzae* and from 15 to 22 for *L. monocytogenes*. This may have affected the data on the relative importance of these pathogens. However, the increase in the number of reporting laboratories for the major pathogens, namely pneumococci, meningococci, GBS and *H. influenzae* was relatively small. Although an additional seven laboratories reported *L. monocytogenes*, the number of cases due to this pathogen was small. In addition, cases of *L. monocytogenes* decreased over the study period, 1983-1999. These data suggest that the increase in the number of laboratories reporting to SCIEH during the study period is unlikely to represent the primary explanation for the reported findings.

5.1.1.3. Case definition

Only cases with isolation of pneumococci, meningococci, GBS, *H. influenzae* and *L. monocytogenes* from CSF isolates were considered as meningitis in the study. Thus, cases without CSF cultures, which were blood culture positive, but with a clinical diagnosis of meningitis, were classified as INMD. In the study of invasive bacterial disease some pathogens are not included in this review, which can also cause bacterial meningitis or INMD. However, based on the previous studies, meningitis is less commonly associated with other bacterial pathogens (less than 15% in the US[490] and between 5% and 9% in the UK[205]) and thus may not have a significant impact on the study results of bacterial meningitis. However, this was not known for INMD due to other bacterial pathogens.

5.1.1.4. Serological testing and antibiotic susceptibility

Although antibiotic susceptibility and serotyping was performed on all isolates submitted to SMPRL, they represent less than 25% of total isolates included in the study. Information on serological and antibiotic susceptibility was presented in less than 5% of cases of pneumococcal disease reported to SCIEH. The establishment of SMPRL in 1992 has improved the data on pneumococcal disease, particularly for serotype distribution and antibiotic susceptibility. The formation of the combined database provides high quality data on pneumococcal disease across Scotland. Nevertheless, 35% and 33% of total invasive and non-invasive isolates, respectively, had serotype information in 1993-99. Data on antibiotic susceptibility ranged from 23% to 44% for penicillin and from 20% to 45% for erythromycin of toal invasive isolates in 1993-99.

The data for resistant isolates may also be over-represented as a result of selectively higher referral by diagnostic laboratories since it is possible that laboratories were more likely to submit antibiotic non-susceptible pneumococcal isolates to SMPRL for confirmation of antibiotic resistance and determination of serotyping. Of the total isolates with serotype information, penicillin and erythromycin susceptibility were tested in 60% and 50% of non-invasive isolates respectively and in 82% and 73% of invasive isolates respectively.

In addition, non-susceptible pneumococcal isolates may have been more likely to be submitted if they were from patients with treatment failure. This may bias the estimates of prevalence of antibiotic non-susceptibility and the distribution of serotypes observed. Thus, the data presented may be unrepresentative of the general picture in Scotland. However, there was no geographical variation in serotype distribution or testing for antibiotic susceptibility across the 15 HBs.

The size of the effect due to these potential biases on the study is not clear. Nevertheless, the annual prevalence of antibiotic non-susceptibility was inconsistent in the study period, suggesting that the increase in antibiotic resistant pneumococci may partially relate to these suggested biases. However, this could equally represent a true temporal variation (Figure 6).

5.1.1.5. Diagnostic methods

The rise in the use of non-cultural diagnostic methods, including latex agglutination, co-agglutination, polymerase chain reaction (PCR) and antigen detection for pneumococci and meningococci in the late 1990s may contribute to the increase in incidence of disease to some extent. For example, a Scottish study showed that cases of meningococcal disease diagnosed by outer membrane protein antibody increased significantly from 7.2% in 1994 to 16.5% in 1999.[491] However, the increase in use of non-culture diagnostic methods may also have led to a decrease in lumbar punctures and thus biased the data on meningitis. Nevertheless, PCR or antibody detection tests would offer an increased likelihood of establishing a positive diagnosis in those who received prior antibiotics.

5.1.1.6. Clinical practices

Changing practices of blood culture and antibiotic administration prior to blood culture may have influenced study results. The implications of these issues on the results of study will be discussed in greater detail in section 5.2.1. No information is available on the changes in clinical practices of blood culture collection and processing procedures for febrile patients in hospitals in Scotland. Similarly, a study in England also reported lack of these data.[103]

5.1.1.7. Vaccine serotypes

Data on coverage of PPVs and PCVs were based on serotypes, assuming that vaccine serotype antigens have cross-reactive protection to other types within that serogroup. Thus, vaccine coverage data may be overestimated.[321,322] Although it is not definitely established, it is generally considered that there is likely to be some degree of cross-protection by vaccine serotype antigens for other types within that serotype.[319] Recent data from the 7-valent PCV trials in US[16] and Finland[17] indicate the possible protection against the 7-valent vaccine-related serotypes within that serotype for both IPD and otitis media.

Data on 14-valent polysaccharide vaccine may seem less relevalent since this vaccine is not in use the UK and most other countries. Nevertheless, data on coverage of this vaccine will be useful for developing conjugate vaccines in the elderly and adults at-risk. At the current time, PCV can be composed of up to 13 serotypes. It is likely therefore that a 14-valent conjugate vaccine may be developed in the future. Thus, data on a 14-valent vaccine is important for developing and guiding policy for high-risk adults.

5.1.1.8. Population estimates

The aggregated population under surveillance for pneumococci and other pathogens was relatively stable in the study period and ranged from 5,100,000 to 5,120,000 approximately. However, there was a decrease in the population under five years of age, from 317,900 in 1983 to 323,000 in 1988 and to 300,817 in 1999 and an increase in the elderly population from 739,800 in 1983 to 757,700 in 1988 and to 784,141 in

1999. The total number of persons with chronic medical conditions such as chronic lung or heart disease also increased in Scotland in the study period.[486] It is likely that population changes, either in age distribution or numbers of people with chronic medical conditions, may affect the study results. Nevertheless, it is difficult to know to what extent the increase in incidence of IPD is due to the increase in the size of these high-risk populations. The incidence of IPD by year and age group was calculated based on the correct population denominators. However, changes in the population with chronic medical conditions were unable to be accounted for in the calculation.

5.1.1.9. Vaccine effect

The present data do not account for the possible effects of pneumococcal and meningococcal polysaccharide vaccines and Hib conjugate vaccine on the incidence of disease. No information is available either on vaccination status or vaccine failures for the study cases. However, from the study survey, the estimated coverage of PPV was 13% among patients with an indication for the vaccine in Scotland. This limited use of PPV among high-risk patients suggests that unknown PPV status and possible vaccine failures among study cases would have little impact on the study results. There is no information on the coverage of meningococcal polysaccharide vaccine in the recommended groups in Scotland but the use of this vaccine appears to be low based on vaccine prescription data and thus may have little effect on the incidence of disease.

Although it is not known individually for the study cases, the coverage of Hib vaccine was over 95% in target groups in Scotland (with known effectiveness of over

90%).[392] This finding is consistent with the results from the present study, which has shown a greater than 90% reduction in meningitis caused by *H. influenzae*.

5.1.1.10. Clinical and other relevant information

No information is available with which to assess the prevalence of specific clinical presentations, underlying medical conditions, life-styles and socio-economic statuses, case-fatality rates and other related outcomes of illness among patients with antibiotic susceptible and non-susceptible IPD. However, these issues are currently being investigated in an ongoing Scottish study (Appendix g).[492]

5.1.2. Survey data

The reliance on self-reported data from respondents is a major limitation of the surveys on PPV. It is possible that rates of PPV coverage in non-respondents may have been lower than those who responded to the surveys. Thus, the study results should be interpreted with some caution.

In survey 1, the HDs were chosen from the hospitals which were selected non-systematically from the NHS in Scotland Directory to be representative of all HDs throughout Scotland. In addition, they were selected non-systematically from personal records. Thus, the data provided by HDs may have a selection bias. Nevertheless, HDs were selected equally from urban and rural hospitals, specialities and grades. This, together with a fair response rate, indicates that the information provided by HDs may be generalisable to all HDs in Scotland.

In survey 2, it is possible that vaccination practices of GPs in the CMR practices may differ from other GPs. However, data on coverage of childhood vaccines were similar in the CMR practices and other general practices in Scotland. This suggests that the results from the CMR survey should be reasonably representative of Scotland as a whole. In addition, data from CMR practices are considered to be correspond to those for the whole of Scotland (section: 3.3.3). The response rate of 85% in this survey also suggests that the results are unlikely to be influenced by respondent-nonrespondent bias. In addition, the response rate in this survey and the survey 1 (60%) were also comparable to the surveys of physician barriers to use PPV in the US, for which response rates were between 52% and 77%.[487,493,494]

In survey 3, the response rate was 72%, similar to a previous UK survey, which determined the use of influenza vaccine in nursing homes.[495] However, only 26% of all nursing homes provided the data on vaccine coverage in the survey. It is therefore possible that vaccine coverage may vary between nursing homes that provided vaccine coverage data and those that did not. There was no difference in vaccine coverage among nursing homes providing vaccine coverage data even when the average number of residents and the presence of immunisation policies were taken into considerations.

In survey 4, coverage for vaccines and antibiotic prophylaxis was determined only for splenectomised patients who are alive. Coverage of these preventive measures may be lower in deceased splenectomised and thus the results may be an overestimate.

5.2. The public health impact of invasive pneumococcal disease

5.2.1. Incidence of invasive disease

A detailed understanding of the local burden of disease is important for informing decisions on the adoption of new vaccines or for prioritising a vaccination programme.[496] This population-based study, with data collected through a national network of diagnostic laboratories covering the entire population of Scotland, demonstrates the burden of IPD in Scotland. These data are necessary to predict the impact of PCV following its inclusion in the UK childhood immunisation programme and to devise effective strategies to increase coverage of PPV in high-risk persons aged 2 years and above.

The mean annual incidence of IPD in Scotland is $9.7/10^5$ population in all ages in the study period. This is similar to the population-based data in England and Wales (9 to $10/10^5$ population),[77,103] Netherlands ($8/10^5$ population)[497] and Finland ($9.1/10^5$ population).[498] The incidence of IPD is lower than that reported from Denmark ($19/10^5$ population),[75] Australia (non-Aboriginal) ($14/10^5$ population),[185] Canada ($15/10^5$ population)[182] and US (22 to $23/10^5$ population).[94,105] Data from Sweden have yielded differing estimates which show wide variation in incidence of invasive disease ranging from 5 to $15/10^5$ population respectively.[99,499,500] It is important to emphasise that these studies differed in their surveillance of IPD that is whether they were passive, active or enhanced surveillance. This should be considered when comparing disease incidence in different countries. Only US[94,105] and Australian[185] studies were based on active laboratory-based surveillance of IPD, which ensures the complete collection of cases of IPD.

There was an increase in the incidence of IPD in Scotland between 1988 and 1999. This finding is consistent with the results of studies from the US in 1978-97,[196] Sweden in 1988-96,[500] Denmark in 1989-94[75] and England and Wales in 1982-92.[501] In contrast, data from Finland[498] showed no increase in IPD. A correlation between blood culture and the incidence of IPD has been previously documented in one UK study.[103] In the study period, there was a 3-fold increased trend in both the total number of blood cultures and the ratio of positive blood to CSF cultures. This increase in blood cultures during the study period is likely to be the cause for an increase in incidence of bacteraemia. This figure also reflects an approximate two-fold increase in the overall incidence of IPD in the study period. Nevertheless, data from Sweden showed that there was a substantial increase in the incidence of IPD without an increase in the number of blood cultures.[502]

It has been postulated that less frequently obtained blood cultures from cases with mild disease may largely relate to under reporting of IPD.[503] This assumption is supported by surveillance data from Chile where blood cultures were usually taken from children with febrile illness, resulting in a two-fold increase in the incidence of IPD.[504] Studies in Europe[75,505] and US[172] observed that the increase in the incidence of IPD was related to an increase in the number of positive pneumococcal isolates from blood cultures. The introduction of a new blood culture system such as BacTAlert in 1996 or automated microbiological procedures for culturing blood may also have some influence on this increase. Other additional factors, which may influence the incidence of bacteraemia, are changes in laboratory and clinicians' diagnostic practices as stated in section 5.1.1. The variation in reported incidence nationally is difficult to interpret whether there is true geographical variation in the incidence of IPD in different locations. In order to understand geographic differences in disease incidence, the establishment of sentinel surveillance systems is required to allow valid comparisons to be made.

It is also possible that the increase in the incidence of IPD over time may relate to the emergence of virulent capsular serotypes in Scotland. It had been suggested that the increase in cases of bacteraemia in Sweden in recent years was due to the newly introduced virulent serotype 14.[506] Valid molecular typing procedures[507] such as multilocus sequence typing (MLST) and multilocus enzyme electrophoresis (MLEE) are required to test this hypothesis.

The peak incidence of IPD was found in young children and the elderly. This confirms the important disease burden of IPD in persons at the extremes of age. IPD has been reported to occur without known high-risk conditions in these two age groups[177] but this remains to be proven in young children.[88] IPD is less common in those aged 2-64 years. The incidence of IPD in young children and the elderly in Scotland is comparable to other developed countries although incidences vary substantially among countries (Tables 3 and 4). Heavy nasopharyngeal colonisation and frequent viral infections in young children may contribute to higher incidence of invasive disease.[152] The presence of chronic medical conditions and waning immunity may relate to increased susceptibility to and mortality from pneumococcal disease in the elderly.[508] In keeping with other studies,[92] the incidence of IPD was found to increase with advancing age, from $27.5/10^5$ persons in aged 65 years and above to $51.5/10^5$ persons in aged 85 years and above. Based on this data, each year, there are at least 215 cases of pneumococcal bacteraemia and meningitis in Scotland and 1420 cases for the whole of UK among the elderly aged 65 years and above. In addition, nearly half of the cases of IPD occurred in this age group in the study although they accounted for only approximately 13-15% of the population.

Although it is not included in the present work, a recent Scottish study has shown that the majority of patients with IPD have underlying medical conditions.[492] The leading high-risk conditions for IPD were coronary artery disease/chronic heart disease, chronic pulmonary disease, non-haematological malignancy, central nervous system disorder and diabetes. A higher case-fatality rate was noted in coronary artery disease/chronic heart disease, hepatic/alcohol abuse and renal disease (Appendix g) as shown in recent data from the US.[94] The overall case-fatality rate of IPD in adults aged 18 to 64 years was 12% in patients with high-risk conditions and 5% in those without high-risk conditions.[94] Case-fatality rate was lowest among children under two years of age (2%) and highest in the elderly 85 years of age and above (40%).[246] It has been documented that more than 62% of deaths due to IPD occurred in persons aged 65 years and above in Scotland in 2000.[492] These data highlight that elderly persons have the highest risk for developing IPD and resultant death. In the future, the public health importance of pneumococcal disease will be significantly greater as the population of elderly people aged 65 years and above is expected to rise in numbers. At present, population based data on the prevalence of underlying medical conditions associated with IPD and their case-fatality rates are lacking in the UK. Such data are essential in deciding correct vaccination policies and systems to provide such data were introduced in Scotland in 2000 (Appendix g).

In common with other studies in the UK,[7] US,[129] Europe[99,498] and Australia (non-indigenous),[509] a higher incidence of IPD was observed in males ($9.4/10^5$) than females ($8.1/10^5$). This difference was noted in both adults and young children.[100,177,181] Although it is not clearly understood, both genetic and behavioural factors may account for these differences in adults. Studies, which adjusted for life-style factors found that the difference between sexes was smaller but a gap remains.[77,204,498,510] The predominant disease related serotypes among males might contribute to this difference but no statistical association between sex and serotype was documented.[511] It has been shown that antibody responses to PPV were lower in males than females,[512] suggesting that females may have greater resistance to disease than males.

The population in Scotland is predominantly Caucasian people. The study data did not provide information on ethnic origin of patients. Nevertheless, the risk of IPD has been documented to be significantly higher in disadvantaged populations such as native (Table 5) or black population compared with white population. This difference may relate to genetic factors and/or poor socio-economic status. However, no deprivation related difference in the incidence of IPD has been seen in Scotland (Appendix g)[492] in contrast to some US studies.[105,132,137] Differences in health care systems may contribute to the conflicting findings on socio-economic status and the risk of IPD. At present, limited data are available on the genetic influence on the development of pneumococcal disease.[513] Further studies are required to elucidate its role in relation to IPD.

The overall incidence of pneumococcal bacteraemia and meningitis was $9/10^5$ population and $0.8/10^5$ population respectively in the study period. The highest incidence of pneumococcal bacteraemia was found in young children less than 2 years of age ($33.1/10^5$ persons) and in the elderly age groups, 65 years of age and above ($27.5/10^5$ persons) and 85 years and above ($51.1/10^5$ persons). Previous studies have shown that the incidence of pneumococcal bacteraemia in young children was 19 to $35/10^5$ persons in the UK, 4 to $24/10^5$ persons in other parts of Europe and 143 to $176/10^5$ persons in the US (Table 3). Incidences of pneumococcal bacteraemia in the elderly ranged from 10 to $80/10^5$ persons in developed countries (Table 4). The factors, which may influence these differences, have been previously discussed (section: 5.1.1). In the study period, the incidence of IPD increased substantially in the elderly (aged 65 years and above) and young children (aged less than 5 years, or less than 2 years) in Scotland. However, a study from Sweden reported that a significant increase in the incidence of pneumococcal bacteraemia occurred in those aged above 60 years but not in children aged less than two years between 1981 and 1995.[177] The overall pattern of both blood cutures and the ratio of blood and CSF cultures increased during the study period in age groups, 65 years and above, less than 2 years or less than 5 years. Thus, it appears that the increase in the incidence of IPD in young children and the elderly is likely to be due to the increased blood culture sampling.

It has been proposed that the increase in the incidence of IPD in children may relate to the disappearance of Hib disease due to the wide spread use of Hib conjugate vaccine.[514] However, no change in the prevalence of carriage[515] and the incidence of IPD[516] was observed among Hib vaccine recipients. There were also no reports on the emergence of epidemic serotypes in Scotland in the study period as noted in

Iceland in 1988-91.[517] Nevertheless this observed increase in the incidence of IPD in young children and the elderly highlights the need for effective pneumococcal vaccines for these two age groups.

Although individuals of all ages can be affected, infants and young children have a higher risk of pneumococcal meningitis. Since the introduction of Hib conjugate vaccine, the pneumococcus has become the leading or second leading cause of bacterial meningitis in children in the UK[518] and US.[188] Consistent with other studies,[177,500,519] the incidence of pneumococcal meningitis remained stable during the study period. The annual incidence of pneumococcal meningitis is greater in young children less than 2 years of age ($11.8/10^5$ persons) than in older age groups, 2 years and above ($< 1/10^5$ persons) in the present study. No increase in the incidence of pneumococcal meningitis was found in the elderly in contrast to bacteraemia. Incidences of pneumococcal meningitis ranged from 2 to $23/10^5$ persons in young children and 0.4 to 3.6 per 10^5 persons in the elderly in population based surveillance in a number of countries (Tables 3 & 4). Differences in the incidence of pneumococcal meningitis are likely to reflect true geographical variation. This is because the completeness of case ascertainment for meningitis is higher since patients with bacterial meningitis require both hospitalisation and positive CSF cultures for diagnosis of meningitis.

The data in this study may still represent underestimates since many febrile patients may not be routinely tested by blood culture. In addition, some cases may be treated in the community or left untreated as previously reported.[520] One US study reported that the risk of occult bacteraemia in febrile children less than 3 years of age who, did not present localising signs, was between 3% and 11%.[521] Blood cultures have been shown to have poor sensitivity for diagnosing pneumococcal pneumonia[522] Studies have shown that 8% to 26% of blood cultures are positive for pneumococci.[101,521,523-525] However, between 15% and 30% of cases of pneumococcal pneumonia have bacteraemia.[92] In addition, patients with pneumonia may not have bacteraemia at the time they present for treatment or when blood cultures are taken. Thus, the true burden of disease due to pneumococci is clearly underestimated in the present study.

Although lung aspiration yields higher sensitivity than blood culture, it is not suitable for routine use[89] and may cause adverse effects.[40,525] The detection of pneumococcal DNA in blood with use of a PCR method can improve the diagnosis of bacteraemic pneumococcal disease[83] but the validity of this method has been questioned.[87] Thus, the lack of a reliable diagnostic method is the major barrier to determine the true burden of pneumococcal disease.[89,526,527] In order to understand the disease burden, some investigators have suggested that studies of hospitalised adults with CAP would provide a good estimate of the burden of disease caused by pneumococci,[92] particularly in relation to health service utilisation. Although there were differences in selection criteria and diagnostic methods for pneumonia, the pneumococcus was the first or the second common cause of pneumonia in these studies.[92] Data from current clinical trials of PCVs would also provide an indirect method for estimating the burden of disease, in particular for culture-negative "hidden" IPD. However, this approach relies on vaccine efficacy and could lead to an underestimate if the vaccine has a low efficacy.

In the present study, there is no information on whether patients received prior antibiotic treatment before cultures have been drawn. One study demonstrated that 5% of blood cultures were positive in those who had prior antibiotic compared with 19% in those who did not receive prior antibiotic treatment.[528] Therefore, these data almost certainly represent an underestimate of the true burden of IPD in Scotland. The development of non-invasive and more sensitive methods of diagnosing pneumococcal disease and the education of health care professionals to carry out blood cultures on febrile patients are essential to document the true impact of the disease.

The prevalence of IPD was clearly related to season in the present study with the highest reported cases in January-March each year, coinciding with the period of peak influenza activity, the period during which it has been shown that pneumococci are isolated more frequently in children.[35,51,156] The seasonal increase in IPD may relate to the concurrent circulation of respiratory viruses in the winter period.[152] Increased activity of respiratory virus activity in winter periods has also been noted as a risk factor for developing pneumococcal pneumonia.[529,530] About 50-80% of pneumococcal pneumonia is thought to be associated with prior occurrence of some form of viral respiratory illness.[529] Viral infections might play a role in facilitating bacterial colonisation and adherence on the epithelial cells, thereby increasing the opportunity for developing bacterial disease.[152]

An additional factor associated with seasonal variation could be related to socio-economic factors among subgroups of susceptible individuals such as the homeless and alcoholics.[156] The present study was unable to assess these life style factors, which have been shown to be associated with the increased risk of disease.[181] This peaked seasonal pattern of IPD could also be indicative of non-invasive pneumococcal pneumonia both in hospitals and in consultations in primary care.[531] The increase in IPD during the winter period emphasises the importance of pneumococcal polysaccharide vaccination as part of the preventive strategy for influenza. This could prevent high-risk patients, particularly the elderly from being admitted to hospital thereby reducing the winter pressure on the NHS.

Since the incidence of pneumococcal bacteraemia and meningitis represent a considerable health problem in Scotland and other countries, an effective strategy to prevent pneumococcal disease, particularly in young children, the elderly and those with underlying medical conditions deserves high public health priority. PPV and PCV are available for the prevention of disease and would offer benefits to these high-risk groups. At present the recommendations for these vaccines are restricted to certain high-risk groups.

Although PPV does not provide protection in children less than two years of age, a new 7-valent PCV is reported to be highly effective in preventing IPD when given along with other childhood vaccines in the US.[532] However, it is not yet included in the routine childhood immunisation programme and is only recommended for children less than two years of age with certain underlying medical conditions in the UK.[21] Although the current recommendations offer benefits to children at highest risk, the universal vaccination of all children less than two years would substantially reduce the overall burden of pneumococcal disease in this age group in the UK.

The current recommendations for PPV are limited to persons aged two years and above, with certain underlying medical conditions, and is not recommended for routine use in the elderly outside these groups.[458] The elderly are the largest single high-risk group for the disease. The use of PPV in the elderly and high-risk patients is not universally accepted,[341] but the WHO, US, Canada and some countries in Europe recommend the routine use of PPV in those aged 65 years and above based on its proven safety, clinical effectiveness (from case-control and indirect cohort studies) and cost-benefit.[15] Although the goal of pneumococcal vaccination is to prevent both bacteraemic and non-bacteraemic pneumococcal disease, its effectiveness in the prevention of bacteraemia alone justifies establishing a policy for the routine use of PPV in the elderly.[533] Thus, the role of PPV in the elderly should be re-evaulated in the UK.

The signficant public health impact of pneumococcal disease described in the present study suggests that utilisation of antibiotics alone cannot reduce the burden of disease in Scotland. Thus, pneumococcal vaccines should be a crucial part of the strategies for prevention of disease in high-risk groups.

5.2.2. Prevalence of antibiotic non-susceptibility

There was an increase in the overall prevalence of penicillin non-susceptible pneumococci in Scotland. It is not consistent in the study period; the prevalence of penicillin non-susceptible pneumococci also increased in different age groups, less than 5 years, 5-64 years and 65 years and above after 1996. Although the study results may have biases to some extent, local knowledge of the prevalence of antibiotic non-susceptible pneumococci is useful for managing pneumococcal disease, minimising the impact of antibiotic use to limit the spread of antibiotic resistance and tracking the impact of intervention outcomes such as programmes increasing PPV coverage and reducing inappropriate antibiotic use.

The prevalence of antibiotic non-susceptible pneumococci is highest among preschool aged children,[246,534] relating to possible excessive antibiotic use, day care attendance and otitis prone condition.[149] In contrast, the level of penicillin non-susceptible isolates was lower in children less than 5 years of age than in the elderly 65 years of age and above in the present study. This suggests that the reporting of invasive isolates may be affected by age. Thus, these data should be interpreted with caution. Nevertheless, the data provide some evidence of the extent of antibiotic non-susceptible pneumococcal disease in Scotland and have been shown to be useful in guiding patient care.[535]

The increase in the prevalence of penicillin and erythromycin non-susceptible pneumococcal isolates in Scotland is of concern since most penicillin non-susceptible isolates are more likely to be multiresistant.[536] In addition, erythromycin non-susceptible isolates have been found to have resistance to other macrolides such as clarithromycin and azithromycin.[537] Thus, choosing the correct antibiotic for treating patients with antibiotic non-susceptible pneumococcal disease becomes challenging. Treatments for invasive and non-invasive pneumococcal disease remain empirical due to the lack of rapid, sensitive and specific diagnostic tests. Decision on antibiotic therapy must be made before diagnostic results are available. Thus, guidelines for empiric therapy decisions in the management of pneumonia[173,538] and otitis media[535] are recommended to take into account the local pattern of antibiotic resistant pneumococci.

Although the prevalence of antibiotic resistant isolates varied with geographical location (Table 6), there was a steady increase in the prevalence of pneumococci resistant to antibiotics worldwide.[238,239] There was a 3-fold increase in the proportion of invasive penicillin and erythromycin non-susceptible isolates in the study period. Surveillance data from England and Wales noted a similar increase in penicillin and erythromycin resistant isolates between 1990 and 1998.[236] A substantial increase in penicillin resistant pneumococci was observed in France (a 43-fold increase from 1986 to 1996), in Japan (a 28-fold increase from 1974 to 1991), and in the US (a 10-fold increase from 1986 to 1997).[539] Improved diagnostic methods in detection of resistant isolates and greater awareness of IPD may in part relate to this increase. However, it is important to note that the determination of the prevalence of resistant pneumococci based on sterile isolates may be biased since isolates obtained from blood or CSF are taken from individuals attending hospital settings. Therefore, nasopharyngeal isolates collected directly from the site associated with person-to-person transmission may be more reliable in detecting the prevalence of pneumococcal resistance in the community.[10]

The prevalence of antibiotic non-susceptible pneumococcal isolates varied among regions in Scotland, ranging from 0% to 27% for penicillin between 1992 and 1999 and from 0% to 55% for erythromycin between 1994 and 1999. The present study indicates that the national prevalence of antibiotic non-susceptibility in pneumococci may not accurately reflect the prevalence of antibiotic resistance within specific regions in Scotland. Thus, specific regional preventive strategies may be required for preventing the spread of antibiotic resistance. Geographical variations in the prevalence of antibiotic non-susceptible isolates are not known but may relate to spread of resistant clones due to the movement of populations.[243,536,540] Differences in populations and study and surveillance methods may also influence the reported variation in the prevalence of antibiotic resistant pneumococci, but these factors are unlikely to explain the regional differences in Scotland. Understanding the factors, which influence these geographical differences in the distribution of pneumococcal resistance could provide clues to prevent the spread of antibiotic resistance.

In the US, the prevalence of antibiotic non-susceptible pneumococci ranged from 7% to 25% for penicillin and from 6% to 15% for erythromycin between 1991 and 1998.[6,195,269,536] In some locations in the US,[541] up to 60% of pneumococcal isolates were resistance to antibiotics. This suggests that the prevalence of resistant pneumococcal isolates may increase steadily once resistant isolates become established in one location. Since a rapid increase in the prevalence of antibiotic resistant pneumococci can occur in a given geographical region, accurate data on antibiotic susceptibility are necessary for timely interventions.

Antibiotic use is generally considered to be directly related to the level of pneumococcal resistance[149] and may influence the difference in rates of resistant pneumococci among different locations.[226] The relationship between antibiotic use and the frequency of resistant pneumococci in the community has been documented.[286,542] The prevalence of antibiotic resistance was lower in Northern than Southern Europe[543] with the reported prevalence of 0% to 5% in Denmark,[180] 1.5% to 3.4% in Sweden[502] and 1% in The Netherlands.[544] An analysis of antibiotic prescription rate per 1000 persons in 13 European countries showed a low utilisation of antibiotics in these countries.[545]

In Scotland, the pattern of antibiotic prescription varied among 15 HBs. Although there was a borderline statistically significant correlation between rates of penicillin prescription and the prevalences of penicillin non-susceptible pneumococci in each HB, this was not observed for erythromycin prescription and the prevalences of erythromycin non-susceptible pneumococci. In addition, the prevalence of penicillin non-susceptible pneumococci was found to correlate with the rate of penicillin (and also erythromycin and all antibiotics) dispensed in Scotland between 1992 and 1999 for age groups less than 5 years and 65 years and above, but not in the age group 5-64 years (although a correlation was noted for erythromycin). Thus, the observed development in the proportion of penicillin and erythromycin non-susceptible isolates is difficult to explain, but may relate to the spread of antibiotic resistant clones.[546] In Scotland, data on the molecular characterisation of penicillin resistance and multidrug resistant pneumococcal isolates are needed to investigate further.

If the observed increase in the prevalence of non-susceptible pneumococcal isolates continues to occur in Scotland, the choice of empiric therapy may be limited for the elderly and those with high-risk conditions who are at greatest risk of death and complications from pneumococcal disease. In the US, the increase in the prevalence of antibiotic resistant pneumococcal disease has led to changes in recommended empiric treatment regimens for pneumococcal meningitis, pneumonia and otitis media.[535,538,547,548] A clear clinical outcome of non-susceptible pneumococci causing both invasive and non-invasive pneumococcal disease is yet to be fully established but some evidence from the US reveals that patients infected with penicillin non-susceptible pneumococcal strains have poor medical outcomes.[6,8,300] Treatment failures associated with antibiotic resistant pneumococci in cases with meningitis and acute otitis media have also been reported, [535,549,550] however, their relationships to pneumococcal pneumonia is less certain and difficult to establish.[267] The clinical impact of resistant pneumococcal disease is difficult to determine due to variations in underlying medical conditions, the degree of resistance and the site of infection.[10] The current prevalence of antibiotic non-susceptibility and lack of a high incidence of clinical failures in Scotland suggest that many antibiotics currently in use may still be appropriate, if used correctly.

Although there have been no apparent outbreaks of pneumococcal disease in Scottish nursing homes in the study period, unrecognised clusters of pneumococcal disease can occur.[140] Outbreaks of pneumococcal disease due to antibiotic susceptible and non-susceptible pneumococci have been reported in overcrowded environments.[140,143,230,287,551] Several factors including host susceptibility, crowding, colonisation with a virulent strain and low PPV utilisation may contribute to outbreaks. These data have important implications for the use of PPV in residents of long-term institutions and the use of PCV for children attending day-care centres to prevent outbreaks of antibiotic resistant pneumococcal disease.

It has been proposed that the observed increase in the diagnostic rate of IPD in the study period should result in selective antibiotic use thereby reducing inappropriate antibiotic use and possible exposure to antibiotic selective pressure and limiting the spread of pneumococcal resistance.[103] However, it is also possible that the increase in the incidence of IPD between 1988 and 1999 in Scotland may, in itself, be due to the reduced antibiotic sensitivity of pneumococci.

The current study suggests that, at present, the level of antibiotic resistant pneumococcal disease in Scotland is low compared with some other countries in Europe and North America. Nevertheless, the pattern of antibiotic resistance increased in the study period, highlighting the need for the constant surveillance of antibiotic resistance in pneumococci. Additional studies are required to determine the clinical, economic and epidemiological impact of antibiotic resistant pneumococcal disease.

5.2.3. Relative contribution of pneumococci to invasive bacterial disease

Bacterial meningitis and other invasive bacterial disease are leading causes of morbidity and mortality in the UK[205,236,552] and other countries.[188,490,553] These diseases are most frequently caused by pneumococci, meningococci, *H. influenzae*, GBS and *L. monocytogenes* with the exception of *Escherichia coli* and *Staphylococcus aureus* in the UK[501] and US.[188,490] Before the widespread use of Hib conjugate vaccine in Europe and US, between 50% and 75% of bacterial meningitis or other invasive bacterial disease was due to Hib in children under 5 years of age.[205,490,553]

Significant changes in the epidemiology of invasive bacterial disease occurred between 1983-91 and 1992-99, before and after the widespread use of Hib conjugate vaccine in Scotland. These include: (1) the incidence of bacterial meningitis due to pneumococci and GBS was stable; (2) pneumococci were the predominant cause of INMD in both periods; (3) the incidence of INMD caused by pneumococci, meningococci and GBS increased by 56%, 27% and 55% respectively; (4) decreases in the incidence of bacterial meningitis by 50% and INMD by 50% due to *L. monocytogenes* were detected; (5) dramatic reductions in the proportions of bacterial meningitis by 92% and INMD by 56% due to *H. influenzae* were documented. Such data together with an understanding of pathogenic agents, pathogen-specific epidemiological trends and at-risk populations are essential in prioritising treatments and preventive interventions and in developing suitable clinical recommendations.

At present, polysaccharide or conjugate vaccines are available for the prevention of disease due to pneumococcal, meningococcal and *H. influenzae* infections.[554,555] Thus, many cases of invasive bacterial disease caused by these pathogens in Scotland could be prevented with use of these existing vaccines. A 50% decrease in bacterial meningitis due to these five pathogens occurred between 1983-91 and 1992-99, before and after the routine use of Hib conjugate vaccine in Scotland. This suggests that a similar result might be achieved if effective conjugate vaccines against pneumococci are available for use in the future. The successful development of GBS conjugate vaccines is another potential prospect for the prevention of invasive bacterial disease since GBS is the principal cause of neonatal sepsis and meningitis.[556]

The proportion of bacterial meningitis and INMD caused by pneumococci, meningococci, *H. influenzae*, GBS and *L. monocytogenes* varied in both developed and developing countries.[557,558] Case-fatality rates of bacterial meningitis ranged from 5% to 40%, with 9% to 30% of survivors sustaining neurological deficits, depending on the infecting pathogen.[188,559,560] It has been reported that pneumococcal meningitis is associated with higher rates of case-fatality[188] and disability than meningococcal or *H. influenzae* meningitis.[211,559]

The pneumococcus was the second most common cause of bacterial meningitis between 1983-91 and 1992-99, accounting for 22.4% and 36.3% of total cases of bacterial meningitis and INMD respectively between 1992 and 1999, highlighting the increasing importance of pneumococci as a cause of bacterial meningitis in Scotland. Surveillance data from Europe[561] and US[188] also showed that the pneumococcus was the predominant cause of bacterial meningitis and other invasive bacterial disease. Approximately 48% of cases of bacterial meningitis were caused by pneumococci in the US[188] and about 30% in Malawi.[562] In the present study, most cases of INMD were due to the pneumococcus, 57% in 1983-91 and 69% in 1992-99, demonstrating the importance of preventing disease associated with this pathogen. Similar to previous studies in the UK[563] and US,[188] changes in age-specific disease trends occurred as a result of the routine Hib conjugate vaccination of infants and young children. These data have important implications for current age-based preventive and treatment guidelines.

Pneumococci caused 24% of INMD and 26% of bacterial meningitis in age groups, less than 1 year and 1-4 years between 1992 and 1999 in Scotland. US multistate pneumococcal surveillance data found that approximately 50% of bacterial meningitis was due to pneumococci in age group 1-23 months.[188] The incidence of bacterial meningitis due to pneumococci ($12/10^5$ persons) was higher than GBS ($8/10^5$ persons), *H. influenzae* ($3/10^5$ persons) and *L. monocytogenes* ($1/10^5$ persons) but lower than meningococci ($23/10^5$ persons) in children less than one year of age in Scotland between 1992 and 1999. The proportion of cases caused by pneumococci increased nearly 2-fold in the age group less than one year between 1983-91 and 1992-99, but no significant increase was observed in the elderly, 65 years and above. In keeping with previous studies,[92,188] the proportion of INMD caused by the pneumococcus was substantially higher than other pathogens in age groups, 45 years and above or 65 years and above. US data show that the incidence of invasive bacterial disease caused by pneumococci in the elderly, (65 years and above), was three-fold higher than GBS, 10-fold higher than *H. influenzae* and 20-fold higher than meningococci or *L. monocytogenes* in 1995.[188] In Scotland, the corresponding difference was nine-fold, 19-fold and over 41-fold between 1992 and 1999. These data identify the pneumococcus as one of the leading causes of invasive bacterial disease in Scotland.

The routine use of meningococcal group C conjugate vaccine since November 1999 has been shown to reduce group C meningococcal disease by 92% to 97% in the targeted age groups in England.[393] This vaccine should therefore impact significantly on the epidemiology of invasive bacterial disease and bacterial meningitis, in particular. Thus, it appears that a programme of pneumococcal conjugate vaccination together with the successful development of vaccines for group B meningococcus and GBS could further reduce the burden of invasive bacterial disease in the UK.

5.3. Implications for vaccine prevention policy and strategies

5.3.1. Invasive pneumococcal disease

Current evidence shows that a relatively small numbers of serotypes cause most disease; less than 11 serotypes in young children and less than 23 serotypes in adults.[4,27,69] The most prevalent serotypes are 14, 9, 19, 6, 23, 1, 3, 4, 7, 8 and 18, accounting for between 82-94% of total invasive isolates in all age groups in Scotland. Thus, if an 11-valent PCV includes all these serotypes, the vaccine could potentially cover over 80% of invasive pneumococcal disease in young children, adults and the elderly. Seroepidemiological studies reported that these serotypes were the most commonly associated with IPD in US, Europe, New Zealand and Australia[69,72,511] but the ranking order of these serotypes differed among developed countries. For example, serotype 14 caused less than 3% of IPD in Spain compared with 13% in Denmark, 17% in US, 22% in Finland and 29% in Belgium.[69] Since the selection of serotypes included in a PCV is limited, the formulation of vaccine would need to be based on the predominant serotypes causing disease targeted for prevention in one geographical location.

In Scotland, the most common serotypes were 14, 6, 19, 23 and 9 in the age group less than 2 years; 14, 6, 23, 19, and 18 in those 5 years and less; 1, 9, 14, 7 and 4 in those 5-64 years and 14, 19, 3, 9, and 23 in those 65 years and above. Serotype 14 was the predominant cause of IPD in all age groups; this is also shown in other studies.[69,72] Serotype 1 was the main cause of IPD in age group 5-64 years, accounting for 13.2% of IPD. Serotype 1 was also associated with outbreaks of pneumococcal disease in adults.[138,144,564,565] It has been reported that the risk of IPD caused by serotype 3 increased in the elderly.[511] In this study serotype 3 was the third leading cause of IPD in the elderly. In accordance with previous findings,[511] serotype 14 was the most important serotype in children aged 5 years and less, accounting for 29% to 32% of IPD in Scotland. These data highlight the variation in contribution of different serotypes to age specific disease incidence and outbreak involvement.

There is evidence to show temporal variations of the important pneumococcal serotypes associated with disease.[566] Earlier data from US show that serotype 12 was the most frequent cause of bacteraemia in patients with pneumonia[136] and associated with outbreaks in both children[567] and adults.[568] This serotype was not a common cause of IPD in Scotland. The relative importance of the 11 most prevalent serotypes varied between 1993 and 1999 in the study. Although serotypes 1, 2 and 3 were predominant causes of bacteraemia during 1950 and 1970,[73,74] they represented less than 5% cases of IPD between 1979 and 1994.[68] However, recent US data indicate that serotypes 1, 3 and 6A are important invasive pathogens, where serotype 1 accounted for 27% of IPD from blood isolates.[569] The potential risk of a shift in serotype distribution raises the possibility of needing to change the components of pneumococcal vaccines, over time, in some geographical locations. This also has important implications for the long-term effectiveness of PCV.

The present study found that serotypes 14, 9, 19 and 6 were the most prevalent causes of IPD in Scotland. Serotypes 6, 14, 18 and 23 were most frequently associated with IPD in the US and other parts of Europe.[69,72] Worldwide data on pneumococcal serotype distribution indicate that serotypes 1 and 5 were those most associated with disease in Asia and Africa,[69,72,503] serotypes 4, 19 and 23 in North America and Europe[511] and serotypes 14, 6 and 19 in all geographical locations.[69] Therefore, the formulation of 9-valent PCV has included serotypes 1 and 5 with the intention of global use.[316] Variations in historical and geographical distribution of pneumococcal serotypes may be due to differences in socio-economic conditions, practice of blood culture sampling for diagnosis, use of pneumococcal vaccine and antibiotics, immunocompromised status and genetic susceptibility of populations;[570,571] but they remain unclear. Such differences impose a major challenge for developing a conjugate vaccine which is suitable for all geographical locations.

The 23-valent and previous 14-valent PPVs included 97% and over 83% of the serotypes responsible for invasive disease respectively in Scotland. Coverage of PPV was similar to other parts of the UK (91-97%),[103,235,572] Sweden (89-97%),[502] Italy (84%),[573] Finland (95%),[498] Denmark (92%),[75] the US (above 85%),[319,363] and Canada (above 90%)[574] for older children and adults. Coverage of PPVs for invasive disease causing serotypes was lower in some Asian countries, between 63% and 75% coverage.[575,576] These data indicate that the vast majority of serotypes causing IPD in Scotland and most other developed countries were included in the formulation of PPVs. In addition, PPV provides broader coverage of disease-causing serotypes than PCVs. If the current 23-valent PPV is indeed 50% to 80% effective against IPD, as estimated by retrospective studies,[1,12] greater use of this vaccine in high-risk adults would prevent a significant proportion of IPD in Scotland.

Studies have shown that coverage of 7-valent PCV vaccine in young children was about 69-79% in the UK[77,179] and between 83% and 86% in the US[68] for serotypes associated with IPD. In some parts of Europe, coverage of 7-valent PCV ranged from 53% to 83 % in children.[539] The 7-valent PCV related serotypes accounted for 70% of invasive isolates in Africa and 46% in Asia.[577] Vaccine coverage in Scotland was above 80% with the 7- and 9-valent PCVs and above 90% with the 11-valent PCV in children less than two years of age. However, coverage of 7-, 9- and/or 11-valent PCVs was substantially lower in age group 5 years and above: 50-57% with 7-valent, 62-63% with 9-valent and 75-76% with 11-valent conjugate vaccines. PPV and PCVs coverage varied from year to year, between 1993 and 1999; the most prevalent serotypes also varied in a similar fashion. This has important implications for the potential effectiveness of pneumococcal vaccine and highlights the need for constant surveillance on pneumococcal serotype distribution.

The most prevalent non-conjugate vaccine serotypes were 8, 11, 12 and 22, accounting for 15.6% and 12.4% of isolates in age group 5-64 years and 65 years and above respectively. The inclusion of these serotypes in the 11-valent conjugate vaccine could increase the coverage of conjugate vaccine to above 80% in these two age groups. In the US, the introduction and routine use of a 7-valent PCV has been documented to reduce the incidence of IPD by 87.3%, 58.1% and 62.4% in children aged less than 1 year, less than 2 years and less than 5 years respectively.[532] Similar results may be achievable if PCV is included in the routine childhood immunisation programme in the UK. The role of PCV against IPD in the elderly and adults with high-risk conditions has yet to be established. At present, PPV offers the potential for prevention of disease in high-risk adults before the availability of new more effective vaccines. A combination schedule of PCV and PPV may induce good immune responses for serotypes included in the PCV and offer a broad coverage to other serotypes in the PPV. Thus, the optimal schedule for immunisation with PCV followed by PPV needs to be investigated.

5.3.2. Non-invasive pneumococcal disease

A reduction in otitis media, lower and upper respiratory infection and acquisition of nasopharyngeal carriage has been documented with pneumococcal conjugate vaccination. Serotype distribution of non-invasive pneumococcal isolates may not be the same as invasive isolates. Understanding serotype distribution and antibiotic resistance patterns in non-invasive pneumococcal isolates would provide important information for vaccine strategies and an estimation of the potential impact of PCVs in the future.

The 11 most common serotypes associated with non-invasive disease were 23, 9, 6, 19, 14, 3, 15, 11, 33, 7 and 10 (in descending order) in Scotland. In common with other reports in the UK[76,572,578] and other developed and developing countries,[78,575] serotypes 23, 9, 6 and 19 were the predominant causes of non-invasive pneumococcal disease. Although serotype 1 was one of the important pathogens for IPD in Scotland and other countries,[577] it was not a common cause of NIPD. This supports the evidence that this serotype is not usually carried in the nasopharynx.[579]

Data on pneumococcal serotypes causing lower respiratory tract infection in young children are less established because of the difficulties in obtaining adequate samples for culture.[580] Over 85% of non-invasive disease was due to 7-, 9- and 11-valent PCVs related serotypes in children aged 5 years and less. Coverage of 7-, 9-, and 11-valent PCVs was lower for older age groups than the age groups less than 2 years and 5 years and less as in other studies.[77,78] Serotypes in all conjugate vaccine formulations were responsible for over 80% of non-invasive disease in children aged less than two years. The serotypes in the 7-, 9- and 11-valent PCV accounted for most invasive and non-invasive disease in children in most parts of the world. Thus, PCV targeted towards young children would not require more than 11 serotypes. The prevalence of non-conjugate vaccines serotypes 15, 11, 33 and 10 were more common in older age groups in Scotland, indicating that conjugate vaccine formulations for adult age groups would ideally require different serotype compositions for the prevention of NIPD in Scotland.

The prevalence of nasopharyngeal carriage with both vaccine serotypes and non-invasive serotypes was reported to be higher in young children than in adults.[51,53] PCVs have been shown to reduce nasopharyngeal carriage of vaccine serotypes, not only in the vaccine recipients but also in their siblings.[309,406] Since there is an association between carriage and the spread of disease, children may be a major source of pneumococci and pneumococcal disease in the community. One US study also shows that exposure to children is a risk factor for IPD in adults.[133] Thus, universal vaccination of young children may extend protection from pneumococcal disease to non-vaccinated individuals by herd immunity.

In the present study, the findings of a similar serotype distribution in both invasive and non-invasive disease, regardless of the site of clinical isolates, is consistent with serotypes colonising non-sterile sites and having the potential to cause invasive disease. Data from Papua New Guinea suggest that serotypes causing upper respiratory tract infection (URTI) could be used to obtain a conservative estimate of susceptibility to invasive pneumococci.[60] Since serotypes associated with NIPD reflect closely those associated with IPD, immunisation would be expected to reduce the risk of both forms of pneumococcal disease. However, this extrapolation is limited to serotypes 1 and 5, important causes of invasive disease and serotype 3, an important cause of otitis media, because they are not usually carried in the nasopharynx.[577] Although the efficacy of 7-valent PCV is lower in non-invasive disease compared with invasive disease, the annual number of cases of non-invasive pneumococcal disease such as otitis media, pneumonia and upper and lower respiratory infections is substantially higher than invasive disease. Therefore, wider use of PCV may reduce significantly the burden of non-invasive disease caused by pneumococci in Scotland. The impact of PCVs on NIPD needs further evaluation.

Although the efficacy of PCVs has yet to be determined in adults, they induce higher antibody responses than PPV in adults, the elderly and persons with immunocompromised conditions.[409,581] This suggests that they may offer better protection in adults with high-risk conditions. In Scotland, the coverage of PCVs was less optimal for both invasive and non-invasive isolates in older age groups, suggesting additional serotypes may need to be included in the PCV for use in adults. However, the possibility of serious adverse events and poorer immunogenicity, due to the inclusion of a large number of serotypes attached to a carrier protein, has raised concerns.[582] Careful evaluation is also needed to determine the potential benefits and cost-effectiveness of PCV in adults compared with the current 23-valent PPV. Further studies are required to investigate these issues.

5.3.3. Control of antibiotic resistance

Local knowledge of the site of infection and serotype distribution can inform antibiotic treatment decisions and preventive measures. Serotypes 6, 9, 14, 19 and 23 (in descending order) were responsible for most cases of invasive penicillin and erythromycin non-susceptible pneumococcal disease in this study; this is similar to findings in other countries.[267] The two high-level resistant invasive isolates from blood were due to serotype 14. In addition, approximately 75% of invasive erythromycin non-susceptible isolates were due to this serotype in Scotland. There were no invasive isolates from CSF which were non-susceptible to penicillin and other antibiotics. A recent Scottish study[492] and US data[583] indicated that serotype 3 was associated with higher mortality. Nevertheless, IPD and NIPD associated with serotype 3 were uniformly susceptible to penicillin and other antibiotics in the study period.

It has been observed that pneumococci carried in the upper respiratory tract are more often resistant to antibiotics than invasive strains.[43,578] Although their rank orders differed, the same serotypes (23, 9, 6, 19 and 14) were most frequently associated with antibiotic resistance among non-invasive isolates, accounting for over 95% of total isolates. These five serotypes are most commonly carried in the nasopharynx.[10,33] As the duration of nasopharyngeal colonisation with these serotypes is longer than with other serotypes,[584] they have higher exposure to antibiotics thereby putting selective pressure on those populations of carried pneumococci. The fact that most resistance is found in these five serotypes also suggests that other pneumococcal serotypes may have more limited ability to acquire resistance genes from the environment. At present, resistance is rare or has not been detected in serotypes more frequently found in adults.[536]

In England and Wales, similar serotypes (23F, 6B, 19A, 19C, 19F and 23F) were identified as the most common cause of antibiotic resistance.[235] Erythromycin resistance was associated with serotypes 3, 5, 9, 14, 19 and 22 in 1990 and serotypes 3, 6, 14, 15, 19 and 23 in 1995.[235] Serotypes 6, 9, and 23 were most frequently associated with penicillin resistance in other UK studies.[272,273,275] Elsewhere, the most prevalent penicillin resistant pneumococci are; serotypes 9 and 23 in Canada,[574,585] 6, 14, 19 and 23 in South Africa, Spain and Hungary[237] and 6B, 9V, 14, 19F and 23F in the US.[195,536] Serotype 14 was reported to have caused an outbreak of multidrug resistant meningitis in a day-care centre [147] and serotypes 23F, 6A and 6B were more likely to be resistant to penicillin in the US.[195] There is also evidence to show that penicillin resistant serotypes were more likely to be resistant to other antibiotics.[269,536] Overall, these data suggest that the pattern of penicillin and erythromycin non-susceptible pneumococcal serotypes was similar in most geographical locations. Nevertheless, serotype 35B in the US,[586] serotype 15 in Spain[587] and serotypes 10, 13 and 16 in Kenya[266,588] have been reported to be associated with penicillin resistance. The appearance of new resistant strains has also been reported in the US in recent years.[589,590] Thus, it is important to monitor the emergence of penicillin resistant strains, their genetic profiles and their frequency and distribution in both adults and young children in the UK using the precise molecular methods currently available.

The 23-valent and previous 14-valent PPVs covered over 98% of invasive isolates resistant to penicillin and erythromycin. Over 99% non-invasive isolates associated with penicillin and erythromycin resistant strains were also included in the 23-valent PPV. More than 94% of penicillin and erythromycin non-susceptible invasive and non-invasive pneumococci were present in the formulation of 7-, 9- and 11-valent PCVs. Thus, the formulation of PPVs and PCVs includes the principal serotypes associated with penicillin and other antibiotic non-susceptible pneumococci in Scotland and in other countries.

The ability of PCVs to interrupt transmission of carriage associated with antibiotic resistant serotypes[309] suggests that these vaccines have the potential to reduce antibiotic resistant pneumococcal disease and the use of antibiotics. In addition, as antibiotic resistance in pneumococci is largely restricted to those serotypes causing a significant proportion of IPD, PCV would offer most benefit to populations with a high prevalence of antibiotic resistance.[406] Furthermore, the effects of PCV on antibiotic resistant pneumococci have implications for the choice of antibiotics for empiric treatment in children with febrile illness if a child is known to have received PCV. The introduction and widespread use of PCV, together with Hib conjugate vaccine, would dramatically reduce the incidence of occult bacteraemia in young children. Changes in strategies for the management of a febrile child may be required after introduction of universal infant immunisation with PCV. However, concerns have been raised as to the possible emergence of antibiotic resistant non-conjugate vaccine serotypes due to serotype replacement.[591]

5.4. Strategies to improve polysaccharide vaccine coverage

Despite the DoH recommendations,[12] the vaccine is underused among high-risk patients in the UK as in other developed countries.[15] The overall vaccine coverage was estimated to be 13% among patients recommended to receive the vaccine by the UK Departments of Health. A substantially higher coverage of PPV (88%) was noted in splenectomised patients. The elderly and persons in nursing homes or other long-term care institutions are not currently included in the general recommendations. Nevertheless, 22% of all elderly (aged 65 years and above) and 11% of elderly home residents received the vaccine. This suggests that elderly persons are more likely to receive the vaccine than other high-risk patients, with the exception of splenectomised patients.

Poor coverage of PPV in high-risk patients may relate to uncertainty regarding the benefits of vaccination, inadequate knowledge of risk and of the impact of pneumococcal disease.[462] It is likely that these factors may affect the use of vaccine by GPs in the UK. The majority of GPs and HDs in the present survey support the use of PPV in high-risk groups and recognise the safety and effectiveness of the vaccine. The US studies have also indicated that physicians in both general practice and hospital settings have adequate knowledge of PPV target groups and its usefulness but they have failed to act on this in clinical practice.[487,592] In addition, in the present study, the majority of GPs considered that the responsibility for pneumococcal polysaccharide vaccination lay with them. Nevertheless, the vaccine was underused among recommended persons in Scotland. However, there was a substantial increase in the distribution of PPV in the whole of Scotland and among the 53 CMR practices in recent years (since 1996). This has also been reported in some developed countries.[15] This pattern of increase in vaccine distribution coincided with the national recommendations issued in 1992[593] and 1996.[458] A review of pneumococcal polysaccharide vaccination polices in North America and Europe also suggests that the presence of recommendations is strongly related to the level of vaccine use and distribution.[15]

Previous UK surveys[13,14] show that coverage of PPV was less than 15% in patients with indications for the vaccine. Current coverage of PPV was very similar to that seen for influenza vaccine coverage in the late 1980s in the UK. Although the target patients for pneumococcal polysaccharide vaccination are almost the same as those for influenza vaccine,[458] there was a remarkable difference in coverage of influenza vaccine and PPV.[13,594] Similar findings are also documented in the US and other developed countries.[1,15,595,596] There was over 1.5-fold difference in coverage of PPV among patients recommended for vaccination in the DoH guidelines, between the data from the survey and an estimated figure based on the total number of patients with vaccine indications and the total number of vaccine distributed in the CMR practices. These data suggest that not all vaccines actually dispensed were used in current target groups. The total number of high-risk patients recommended for PPV, according to the DoH criteria, in the whole of Scotland was about 420,000 patients. If all elderly aged 65 and above were included in the vaccine recommendations, this number would increase 3-fold, to about 1,200,000. This indicates that a policy to extend pneumococcal polysaccharide vaccination to all elderly would elevate costs significantly, although the use of PPV in high-risk groups - especially the elderly -

may yet be economically justifiable.[441,597] The increased risk of IPD in the elderly documented in the present study results (section: 5.2.1) and previous studies (Table 4), together with a substantial body of evidence of PPV effectiveness against IPD in the elderly from the retrospective studies (Table 9), also support the administration of PPV to all elderly aged 65 years and above. Although there is absence of data on the effectiveness of PPV in the prevention of pneumococcal pneumonia in the elderly from the meta-analyses and RCTs, Fedson[598] has argued that clinicians do not need to know whether the vaccine is clinically - or cost-effective in preventing pneumococcal pneumonia. The decision to use PPV in the elderly or patients with high-risk conditions should be based on the demonstrated risk and effectiveness of PPV against IPD in these at-risk groups.

UK studies have shown that influenza vaccine was three-fold more likely to be recommended than PPV.[599,600] It is also clear from the survey that among both GPs and HDs acceptance of influenza vaccine was higher than PPV. Unlike influenza vaccination, PPV may be given opportunistically at any time of year. At present, many opportunities have been missed to offer PPV during annual influenza vaccination. It appears that the protective benefits of pneumococcal polysaccharide vaccination have been largely undervalued by GPs. The lower levels of PPV coverage in high-risk patients, compared with influenza vaccine coverage may, in part, relate to this. GPs and HDs in the survey had suboptimal knowledge of vaccine safety and effectiveness for patients who are elderly, immunocompromised or have other underlying medical conditions. In addition, the study findings also showed that HDs were less likely than GPs to know whether PPV was safe and effective in high-risk patients. Since many patients come into contact with HDs during their hospitalisations and outpatient visits, this lack of knowledge about PPV could lead to missed opportunities for vaccination in hospital settings. Thus, there is a need for an education programme on adult vaccine preventable diseases in medical training. Further problems are indicated by US studies which found that adult vaccination was a low priority among physicians.[138,551]

The factors related to poor use of PPV in single-handed and rural practices are difficult to determine from our survey. Reasons may include greater workload or other factors which require further investigation. To determine whether this might be due to a disproportionate number of high-risk patients such as those with chronic heart and lung conditions in urban areas, further data on the number of patients with chronic heart disease and chronic obstructive pulmonary/lung disease in both urban and rural areas from the CMR system, ISD, were extracted. If the patient population in urban practices had higher proportions of such individuals, it might be expected that GPs would have a greater knowledge of PPV for such conditions. The data showed that there was a difference in the proportion of patients with chronic heart disease (rural=25/1,000 population; urban=21/1000 population) and chronic pulmonary disease (rural=57/1000 population; urban 42/1000 population) in rural versus urban areas. Thus, it appears that differences in the use of PPV in rural and urban area GPs are unlikely to relate to the proportion of such patients in the survey but may partly relate to the higher prevalence of policies on PPV among urban or group practices.

Epidemiological studies have shown that more than two-thirds of persons with serious pneumococcal disease had previous hospitalisation in the preceding 3-5 years.[601] Studies in the US have consistently reported that hospital-based influenza and pneumococcal polysaccharide vaccination programmes during outpatient visits or at hospital discharge are effective means of increasing coverage of the vaccine, [480,602] and should be considered as a complementary strategy to a primary care based vaccination programme in the UK. Only 2% of patients in Scotland, with vaccine indications, had ever received PPV in the hospital setting. This suggests that very little effort has been made to improve coverage of PPV by health care workers in hospital. Moreover, as persons with chronic medical conditions are more likely to use other health care services and long-term care institutions, the initiation of pneumococcal polysaccharide vaccination programmes in nursing homes and other medical care facilities could improve the coverage of PPV in high-risk patients. The results also indicated that vaccination programmes organised by nursing staff were considered to be an effective strategy for improving coverage of PPV. Use of standard order for nurses would ease the administration of adult vaccines in hospital settings and long-term care facilities.[603]

While about half of nursing homes expressed the view that the presence of systematic immunisation records would increase vaccine coverage, only 6% of homes reported having such records. This finding has implications for the use of PPV because of misconceptions about the risk of adverse reactions following revaccination.[604] Thus, lack of systematic recording for PPV may inhibit the vaccination. US studies have reported that the determination of PPV status of patients is difficult.[142,551] However, as a second dose of PPV does not appear to be associated with serious adverse effects,[338,384] it is recommended that PPV should be given to patients with unknown vaccination history,[1,91] while improvements in systematic recording of adult immunisation may not only increase vaccine coverage, but also inform the timely revaccination of some high-risk patients. Indeed, there is evidence to show that the level of antibody and protection by PPV may decline over time.[604] Thus, compliance with the DoH guidelines for revaccination of certain high-risk patients at the appropriate interval may lower the risk of IPD in the recommended groups.

The most common reasons for non-receipt of PPV included lack of awareness and failure to receive a recommendation from a GP in Scotland. It has been found that 77% and 15% of PPV recommended patients had not received the vaccine due to these two reasons respectively.[14] Most reported reasons for receiving PPV were recommendations from GPs and other members of primary health care teams in the present surveys. Previous studies from the UK and US revealed that 85% of PPV recipients were immunised on the basis of advice from health care workers.[14,603] These data highlight the pivotal role of health care workers in determining coverage of PPV. Previous studies have also shown that lack of awareness of the vaccine and the risk of disease are the most important reasons for not receiving the vaccine.[605-608] Surveys in the UK and US showed that between 73% and 91% of vaccine recipients were immunised due to physician advice.[14,551] In common with previous findings,[609] difficulty in obtaining consent on behalf of mentally incompetent patients was indicated to be one of the important barriers to pneumococcal polysaccharide vaccination in nursing home residents. A Canadian study has indicated that obtaining consent for vaccination on admission for current and future years can increase the coverage of PPV.[610]

The nursing home survey showed that the main factors in non-receipt of PPV included refusal of vaccine by residents or family members, or no specific reason. In addition, there was an association between the deprivation category of high-risk patients and the coverage of PPV. However, no relationship was observed between deprivation category status and the coverage of recommended vaccines or antibiotic prophylaxis in splenectomised patients. Data from the US also indicates a relationship between low socio-economic status and poor vaccine coverage in children[611] and adults.[606] These data suggest that although strategies to improve vaccine acceptance behaviours may particularly need to focus on persons in lower socio-economic status, efforts are equally necessary for those in higher socio-economic status. GPs and HDs in the survey felt that a public health campaign on awareness of pneumococcal vaccine could increase the coverage of vaccine. A UK study has demonstrated that an organised public campaign of pneumococcal polysaccharide vaccination can increase coverage of vaccine, from 4.5% to 19.5% among high-risk patients and use of vaccine among GPs, from 17% to 89%.[13] Education programmes aimed at both health care professionals (doctors, nurses and pharmacists) and patients, improved practice guidelines and effective methods to identify high-risk patients such as letter/postcard/chart/computer reminders may help increase the likelihood of vaccine uptake.[603]

Differences in the existence of influenza and pneumococcal polysaccharide vaccination policies and vaccine coverage highlight the need for improved guidelines and policies from the UK Departments of Health. At present, there is no set target for pneumococcal polysaccharide vaccination in the UK. In the US, a national objective has been set to achieve over 90% coverage of PPV in all elderly, residents of long-term care facilities and other high-risk persons by the year 2010.[612] Recommendations that provide the potential way to enhance vaccine coverage in adults have been issued in the US recently.[603] GPs and HDs in the survey reported that clear immunisation guidelines were essential in improving PPV coverage. The current chronic disease-based pneumococcal polysaccharide vaccination policy is not well defined and requires clarifications of specific indications for vaccination such as chronic lung or heart disease, which are yet unclear. Age-based strategies are more successful in increasing vaccine coverage than patient-selection strategies based on medical conditions.[596] Nevertheless, the coverage of PPV was lower in the age group less than 65 years compared with the age group 65 years and above, suggesting that greater attention is required to vaccinate the non-elderly with chronic medical conditions. Although PPV is recommended two weeks prior to elective splenectomy,[458,613] the adherence to this guideline was poor among GPs and other clinicians. As PPV is likely to induce better antibody responses if given before splenectomy,[614] improved guideline adherence is needed to ensure that elective splenectomised patients receive the vaccine at the appropriate time.

At present, there are no payment mechanisms for pneumococcal polysaccharide vaccination in Scotland. Over 80% of GPs and HDs suggested that financial support and incentive payments for PPV could increase its use, suggesting that lack of financial support may discourage the utilisation of PPV among GPs in Scotland. If funding were made available and targets established for adult vaccination similar to those for childhood vaccination, coverage of PPV might improve. The adoption of universal use of influenza vaccine by the UK Departments of Health[468] in all elderly with fees payable to GPs has been an important step toward improving the coverage of influenza vaccine. A gradual increase in the coverage of influenza vaccine, from 45% in 1988-89[615], to 67% in 1991-92[616], to 77% in 1995-96[617] and to 89% in

1998-99[495] in the elderly and persons in long-term care facilities, may relate to payment for influenza vaccination in the UK. Consideration should be given to extending this scheme to cover combined influenza and PPV targets. The extent to which financial incentives and disincentives impact on adult vaccination coverage should be investigated to assess how far improved vaccine coverage could be achieved with reimbursement policies. Establishing appropriate guidelines, audit and feedback on performance may have a positive impact on improving coverage of PPV in the future.

Additional studies in understanding the factors associated with the reasons for receipt and non-receipt of vaccine among high-risk patients and clinicians' vaccine preventable behaviours would aid in developing appropriate vaccination strategies.

6. CONCLUSIONS

This study has confirmed the substantial and increasing disease burden from pneumococcal disease and the rise in prevalence of antibiotic non-susceptibility among pneumococci in Scotland. Although the use of PPV has increased in Scotland, its use in recommended high-risk groups remains low.

The risk of IPD is highest in young children and the elderly. The incidence of pneumococcal bacteraemia was high in these two groups, but this was not observed for pneumococcal meningitis in the elderly. Males had a higher incidence of both bacteraemia and meningitis than females. The peak activity of IPD was observed during winter periods and corresponded with the pattern of influenza activity. There was a 3-fold increase in the prevalence of antibiotic non-susceptibility for penicillin between 1992 and 1999 and for erythromycin between 1994 and 1999. The observed regional difference in the prevalence of antibiotic non-susceptibility correlated weakly with the rate of penicillin prescription in Scotland. A statistically significant correlation was noted between the annual prevalence of penicillin non-susceptibility and the rate of penicillin prescription for age groups, 5 years and less and 65 years and above but not for the age group 5-64 years.

The pneumococcus was the second leading cause of bacterial meningitis and the first cause of INMD in 1992-99, the period after the routine use of Hib conjugate vaccine in Scotland. The proportion of cases of bacterial meningitis due to pneumococci increased nearly 2-fold in the age group less than one year from the period 1983-91 to 1992-99, but no significant increase was recorded for the elderly aged 65 years and above. Over 82% of cases of INMD in the elderly were due to pneumococci between 1983 and 1999.

The present data and those from other parts of the UK indicate that the formulation of all current pneumococcal vaccines includes the predominant serotypes associated with IPD and NIPD. Nearly all serotypes associated with invasive and non-invasive antibiotic resistant pneumococcal disease were also included in the formulation of PPVs and PCVs. Serotypes in the 23-valent and previous 14-valent PPVs accounted for a significant proportion of disease in all age groups. Coverage of PCVs was substantially higher in young children but lower in those above 5 years of age. The annual pattern of the most prevalent serotypes varied between 1993 and 1999. In addition, coverage of PCVs fluctuated markedly from year to year, but this was not observed for PPVs. This highlights the critical importance of monitoring serotype distribution to track changes overtime, both before and after full PCV implementation in the UK.

Overall, these data indicate that the availability of PCV for young children and the increased use of PPV in the elderly and adults with high-risk conditions would reduce significantly the morbidity and mortality associated with antibiotic susceptible and non-susceptible pneumococcal disease in Scotland. In addition, guidelines for clinicians to use antibiotics judiciously, an education programme aimed at the public on the implications of their unnecessary use in the emergence of resistant pneumococci and the availability of pneumococcal vaccines for disease prevention are important in containing resistance.

Although PPV is recommended by DoH for preventing IPD in high-risk groups, the majority of these individuals have not received the vaccine in Scotland. No single factor was documented to account for the low use of PPV. Nevertheless, in recent years, the distribution and use of the vaccine have been improved in Scotland. The majority of GPs and HDs had adequate knowledge with regard to pneumococcal polysaccharide vaccination. Thus, it appears that they may have failed to utilise this knowledge in clinical practice. Most respondents in the surveys also felt that GPs should take the responsibility for providing pneumococcal polysaccharide vaccination. Nearly all patients who received PPV in the present study were vaccinated in general practice. Recommendations from GPs and community nurses were the principal reason for the receipt of PPV. These data highlight the important role of GPs and other members of the primary care team in improving coverage of PPV.

Intensified efforts are required to improve PPV coverage in patients with an indication for the vaccine. The extension of universal targeting of PPV to all elderly, as with the influenza vaccine, is worthy of consideration since this would offer efficiencies in terms of cost benefits and simpler logistics for delivering two preventive measures in one routine surgery visit. This also offers the opportunity to vaccinate at the time of annual influenza vaccination, which has been recognised as the most efficient strategy to delivery PPV. Unlike influenza vaccine, PPV generally lasts for 5 to 10 years. This, together with the results from this study, highlights the need for improved systematic immunisation records in adults. Accurate vaccination status is particularly relevant for some high-risk patients for whom timely revaccination could be important. In Scotland, accurate detailed information on the immunisation status of children for vaccines recommended through the routine immunisation schedule are available through the Standard Immunisation Recall System and the Grampian Immunisation Recall System. Such system should also be introduced for PPV and other vaccines recommended for adults.

Clear national recommendations, reimbursement policies, identification of vaccine eligible patients through computer systems or during routine consultation and organised education and national campaign of vaccination were identified as the important strategies to improve the coverage of PPV. At present, there is no national coverage target for PPV in the UK. Such an objective, together with more specific vaccination policies and clear recommendations for the indication of vaccine in high-risk adults, is probably the most effective way to increase coverage of PPV. The most common reason for non-receipt of PPV was refusal by patients or family members, or no specific reason. Thus, clinicians in both general practice and hospital settings should ensure that their patients are aware of the risk of pneumococcal disease and the benefits of vaccination.

The results from the present study should provide important data for developing appropriate strategies for vaccine policy and delivery of PPV for the prevention of pneumococcal disease in Scotland. Since vaccination against pneumocooci is the major means available to prevent pneumococcal disease, use of PPV and PCV in high-risk groups can yield significant public health benefits. Improved continual surveillance of pneumococci is an essential component of public health efforts to inform the development of appropriate vaccination strategies to prevent antibiotic susceptible and non-susceptible pneumococcal disease.

7. RECOMMENDATIONS

At present, information on serotype and antibiotic susceptibility level is included in less than 5% of laboratory reports reported to SCIEH, although data gained by the SMPRL from its own sources and local laboratory sources results in a dataset containing approximately 70% serotype and antibiotic susceptibility information. The establishment of SMPRL in 1992 has clearly enhanced the data on serotypes distribution and antibiotic susceptibility in Scotland but this still needs to improve in order to inform vaccine policy and to monitor the impact of pneumococcal conjugate vaccination programme. In order to address this issue, enhanced pneumococcal surveillance was established in November 1999, in a collaboration between SCIEH and SMPRL in Scotland. Confirmation of pneumococci, serotyping and antibiotic susceptibility are performed for all isolates submitted to SMPRL from all diagnostic laboratories in Scotland. A single national database has now been established by combining pneumococcal case information or isolates received at SCIEH and SMPRL on a regular monthly basis. In addition, information on demographic characteristics, clinical presentations, underlying medical conditions and outcome of illness in individual cases are now being followed up actively by a surveillance co-ordinator. However, population-based and active pneumococcal surveillance require to be extended to determine the accurate burden of disease and antibiotic resistance. In addition, there is a need for complementary data on pneumococcal isolates associated with important non-invasive disease such as otitis media and pneumonia in Scotland. Local knowledge of pneumococcal isolates causing both invasive and non-invasive disease can provide important strategic data for future vaccination policies and other preventive measures. It is also important to know precisely how diagnostic laboratories select samples for serotyping and antibiotic susceptibility testing. This would help to assess sources of potential bias in relation to accurate determination of the disease burden, serotype distribution and the prevelance of antibiotic non-susceptibility in Scotland.

Since PCV offers serotype specific protection, a reduction in carriage of these serotypes could mean than their ecological niche may be replaced with non-vaccine serotypes.[432] Replacement of vaccine serotypes with non-vaccine serotypes[309] and an increase in otitis media due to non-vaccine serotypes[17] have been reported. To date, there has been no increase in IPD associated with non-vaccine serotypes. In addition, capsular switching promoting virulence of pneumococcus has also been detected.[618] This raises theoretical concerns that the virulence and capsular type of pneumococci may change in response to conjugate vaccine,[591] posing a potential threat to vaccinated persons who are protected against carriage of vaccine type.[432] This presents a potential public health problem. Although all pneumococcal isolates received at SMPRL were serotyped, the population-based genetics of pneumococcus is poorly understood in Scotland. The detection of capsule switching through genetic recombination, (i.e the transfer of genetic determinants that specify pneumococcal capsular polysaccharide), is possible using MLST.[507] This technique can provide clear evidence for a history of recombination in pneumococci.[507] The availability of MLST in Scotland in the future is important for the management and understanding of antibiotic resistance, the selection of appropriate serotypes for vaccine formulation and the long-term epidemiology of pneumococcal disease.

Studies in the US have reported important developments in the understanding of IPD linked to several demographic and epidemiological factors.[6,8,129,132,133,137,140,300] These include (i) the increased risk of IPD in both smokers and HIV-infected persons (ii) the increased occurrence of antibiotic resistance in persons with higher socio-economic status (iii) the poor medical outcomes in persons infected with antibiotic resistant pneumococci and (iv) the increase in reports of outbreaks of pneumococcal disease in long-term care facilities. These new epidemiological associations have implications for prevention of pneumococcal disease in the US, in particular for correct targeting of polysaccharide and conjugate vaccines in high-risk groups.[2,91] Thus, there is a clear need to update the accurate epidemiological features of pneumococcal disease and to identify the distribution of risk factors in the Scottish population.

In order to investigate the current epidemiological features of IPD in Scotland, a record linkage study has been established. This method used data on cases of laboratory confirmed IPD which were linked to the data from both Scottish Morbidity Records and mortality records from the General Register Office for Scotland. These data were used to examine the incidence of disease, antibiotic resistance, serotype distribution, predisposing factors (underlying medical conditions and socio-economic status), clinical presentation, diagnosis, resource use and outcome of IPD. Such record linkage is a powerful epidemiological tool for ascertaining the burden of IPD in Scotland more accurately than previously reported and will allow a detailed study of associations between patients and the epidemiological behaviour of pneumococci to be carried out. In the future, this methodology should be proposed as an essential part of routine surveillance for IPD, including monitoring the effects of vaccination on its epidemiology.

The use of reminder systems such as postcards, letters or telephone calls can help in improving vaccination coverage among high-risk patients. Since the majority of hospitalised patients have recognised indications for PPV, interventions to improve the coverage of PPV should be introduced in hospital care settings to complement the current primary care based vaccination in the UK. A greater understanding of the reasons for vaccination and issues relating to vaccine safety and effectiveness among high-risk patients are key to increasing coverage of PPV. Thus, organised education and vaccination campaigns for PPV are necessary for promoting awareness among the public and for changing clinical practice, knowledge and attitudes of health care professionals.

Clinicians, particularly those in primary care, should make greater efforts to ensure that their patients understand the risks of disease and the benefits of vaccination. The implementation of a standing order for nurses to administer PPV, the presence of a vaccination policy with appropriate targets set and the introduction of an age-related vaccination policy should also enhance vaccine delivery and coverage among patients for whom PPV is recommended. Such interventions should narrow the gap between the policy and practice of pneumococcal polysaccharide vaccination in the UK.

Although the results suggest areas for improving coverage of PPV, further research into the factors associated with clinicians' and patients' preventive behaviours on utilisation of PPV would identify additional barriers for acceptance of vaccination.

8. REFERENCES

1. MMWR. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunisation Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 1997;46:1-24.
2. MMWR. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunisation Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2000;49. No. RR-9:1-38.
3. Sheppard D, Bartlett K, Lampiris H. *Streptococcus pneumoniae* transmission in chronic-care facilities: description of an outbreak and review of management strategies. *Infect Control Hosp Epidemiol* 1998;19:851-853.
4. Klein DL. Pneumococcal disease and the role of conjugate vaccines. *Microb Drug Resist* 1999;5:147-157.
5. World Health Organisation (WHO). Vaccine research and development: report of the technical review group meeting, June 9-10, 1997. Geneva: WHO, 1997:32-36.
6. Plouffe JF, Breiman RF, Facklam RR, et al. Bacteraemia with *Streptococcus pneumoniae*: implications for therapy and prevention. *JAMA* 1996;275:194-198.
7. Laurichesse H, Grimaud O, Waight P, et al. Pneumococcal bacteraemia and meningitis in England and Wales, 1993 to 1995. *Communicable Disease and Public Health* 1998;1:22-27.
8. Feikin DR, Schuchat A, Kolczak M, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995-1997. *Am J Public Health* 2000;90:223-229.

9. Jones R, Pfaller M. Bacterial resistance: a worldwide problem. *Diagn Microbiol Infect Dis* 1998;31:379-388.

10. Schrag SJ, Beall B, Dowell S. Resistant pneumococcal infections: World Health Organization, 2001.WHO/CDS/DRS/2001.6.

11. Friedland I, McCracken G. Management of infections caused by antibiotic-resistant *Streptococcus pneumoniae*. *NEJM* 1994;331:377-382.

12. Fedson DS. The clinical effectiveness of pneumococcal vaccination: a brief review. *Vaccine* 1999;17 (Suppl 1):S85-S90.

13. McDonald P, Friedman E, Banks A, Anderson R, Carman V. Pneumococcal vaccine campaign based in general practices. *BMJ* 1997;314:1094-1098.

14. Kyaw MH, Nguyen-Van-Tam J, Pearson J. Family doctor advice is the main determinant of pneumococcal vaccine uptake. *J Epidemiol Community Health* 1999;53:589-590.

15. Fedson DS. Pneumococcal vaccination in the United States and 20 other developed countries, 1981-1996. *Clin Infect Dis* 1998;26:1117-1123.

16. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* 2000;19:187-195.

17. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *NEJM* 2001;344:403-409.

18. Palmu AAI, Kilpi TM, Jokinen J, et al. Further characterisation of efficacy of a heptavalent pneumococcal conjugate vaccine (PNCCRM) against otitis media. 19th Annual Meeting of the European Society for Paediatric Infectious Diseases; March 2001;Istanbul;2001:22.

19. Dagan R, Sikuler-Cohen M, Zamir O, et al. Effect of a conjugate pneumococcal vaccine on the occurrence of respiratory infections and antibiotic use in day-care centre attendees. *Pediatr Infect Dis J* 2001;20:951-958.

20. Eskola J. Immunogenicity of pneumococcal conjugate vaccines. *Pediatr Infect Dis J* 2000;19:388-393.

21. Department of Health (DoH). Extending meningitis C vaccine to 20-24 years olds; pneumococcal vaccine for at-risk under 2 years olds: Department of Health, 2002:http://www.doh.gov.uk/cmo/cmo0201.htm.

22. Tomasz A. Surface components of *Streptococcus pneumoniae*. *Rev Infect Dis* 1981;3:190-211.

23. Sorensen U, Henrichsen J, Chen HC, Szu S. Covalent linkage between the capsular polysaccharide and the cell wall peptidoglycan of *Streptococcus pneumoniae* revealed by immunochemical methods. *Micro Pathog* 1990;8:325-334.

24. Tuomanen EI, Austrian R, Masure HR. Pathogenesis of pneumococcal infection. *NEJM* 1995;332:1280-1284.

25. Henrichsen J. Six newly recognised types of *Streptococcus pneumoniae*. *J Clin Microbiol* 1995;33:2759-2762.

26. Knecht J, Schiffman G, Austrian R. Some biological properties of pneumococcus type 37 and the chemistry of its capsular polysaccharide. *J Exp Med* 1970;132:475-487.

27. Lee CJ, Banks SD, Li JP. Virulence, immunity, and vaccine related to *Streptococcus pneumoniae*. *Crit Rev Microbiol* 1991;18:89-114.

28. Musher DM. *Streptococcus pneumoniae*. In: Mandell GL, Bennett JE, Raphael D, editors. *Principles and practice of infectious diseases*. First edition: Philadelphia, Pennsylvania, Churchill Livingstone, 1995:1811-1826.

29. Bruyn GW, Zegers B, van Furth R. Mechanisms of host defence against infection with *Streptococcus pneumoniae*. *J Infect Dis* 1992;14:251-262.

30. Musher D, Chapman A, Goree A, et al. Natural and vaccine-related immunity to *Streptococcus pneumoniae*. *J Infect Dis* 1986;154:245-256.

31. Dillard J, Vandersera M, Yother J. Characterisation of the cassette containing genes for type 3 capsular polysaccharide biosynthesis in *Streptococcus pneumoniae*. *J Exp Med* 1995;181:973-983.

32. Garcia E, Arrecubieta C, Munoz R, et al. A functional analysis of the *Streptococcus pneumoniae* genes involved in the synthesis of type 1 and type 3 capsular polysaccharides. *Microb Drug Resist* 1997;3:73-88.

33. Ghaffar F, Friedland IR, McCracken GH. Dynamics of nasopharyngeal colonisation by *Streptococcus pneumoniae*. *Pediatr Infect Dis J* 1999;18:638-646.

34. Black S, Shinefield H. Issues and challenges: pneumococcl vaccination in paediatrics. *Pediatr Ann* 1997;26:355-360.

35. Loda F, Collier A, Glezen W, et al. Occurrence of *Diplococcus pneumoniae* in the upper respiratory tract of children. *J Pediatr* 1975;87:1087-1093.

36. Zenni M, Cheatham S, Thompson J, et al. *Streptococcus pneumoniae* colonisation in the young child: association with otitis media and resistance to penicillin. *J Pediatr* 1995;127:533-537.

37. Hansman D, Morris S, Gregory M, McDonald B. Pneumococcal carriage amongst Australian aborigines in Alice Springs, Northern Territory. *J Hyg (Lond)* 1985;95:677-684.

38. Leach A, Shelby-James T, Mayo M, et al. A prospective study of the impact of community based azithromycin treatment of trachoma on carriage and resistance of *Streptococcus pneumoniae*. *Clin Infect Dis* 1997;24:356-362.

39. Ussery XT, Gessner BD, Lipman H, et al. Risk factors for nasopharyngeal carriage of resistant *Streptococcus pneumoniae* and detection of a multiply resistant clone among children living in the Yukon-Kuskokwim Delta Region of Alaska. *Pediatr Infect Dis J* 1996;15:986-992.

40. Adegbola R, Falade A, Sam B, et al. The aetiology of pneumonia in malnourished and well-nourished Gambian children. *Pediatr Infect Dis J* 1994;13:975-982.

41. Lloyd-Evans N, Dempsey TJO, Baldeh I, et al. Nasopharyngeal carriage of pneumococci in Gambian children and in their families. *Pediatr Infect Dis J* 1996;15:866-871.

42. Gratten M, Gratten H, Poli A, et al. Colonisation of *Haemophilus influenzae* and *Streptococcus pneumoniae* in the upper respiratory tract of neonates in Papua New Guinea: primary acquisition, duration of carriage and relationship to carriage in mothers. *Biol Neonate* 1986;50:114-120.

43. Montgomery J, Lehmann D, Smith T, et al. Bacterial colonisation of the upper respiratory tract and its association with acute respiratory tract infections in Highland children of Papua New Guinea. *Rev Infect Dis* 1990;12 (Suppl 8):S1006-S1016.

44. Austrian R. Some aspects of the pneumococcal carrier state. *J Antimicrob Chemother* 1986;18 (Suppl A):35-45.

45. Anderson B, Dahmen T, Frejd T, et al. Identification of an active disaccharide unit of a glycoconjugate receptor for pneumococci attaching to human pharyngeal epithelial cells. *J Exp Med* 1983;158:559-570.

46. Huebner RE, Dagan R, Porath N, Wasas AD, Klugman KP. Lack of utility of serotyping multiple colonies for detection of simultaneous nasopharyngeal carriage of different pneumococcal serotypes. *Pediatr Infect Dis J* 2000;19:1017-1020.

47. Gray B, Turner M, Dillon HJ. Epidemiologic studies of *Streptococcus pneumoniae* in infants: the effects of season and age on pneumococcal acquisition and carriage in the first 24 months of life. *Am J Epidemiol* 1982;116:692-703.

48. Musher D. Infections caused by *Streptococcus pneumoniae*: clinical spectrum, pathogenesis, immunity and treatment. *Clin Infect Dis* 1992;14:801-809.

49. Aniansson G, Alm B, Anderson B, et al. Nasopharyngeal colonisation during the first year of life. *J Infect Dis* 1992;165 (Suppl 1):38-42.

50. Dagan R, Melamed R, Muallem M, Piglansky L, Yagupsky P. Nasopharyngeal colonisation in southern Israel with antibiotic-resistant pneumococci during the first 2 years of life: relation to serotypes likely to be included in pneumococcal conjugate vaccines. *J Infect Dis* 1996;174:1352-1355.

51. Gray B, Converse G, Dillion HJ. Epidemiologic studies of *Streptococcus pneumoniae* in infants: acquisition, carriage, and infection during the first 24 months of life. *J Infect Dis* 1980;142:923-933.

52. Syrjanen RK, Kilpi TM, Kaijalainen TH, Herva EE, Takala AK. Nasopharyngeal carriage of *Streptococcus pneumoniae* in Finnish children younger than 2 years old. *J Infect Dis* 2001;184:451-459.

53. Hendley J, Sande M, Stewart P, Gwaltney MJ. Spread of *Streptococcus pneumoniae* in families. Carriage rates and distribution of types. *J Infect Dis* 1975;132:55-61.

54. Ingvarsson L, Lundgren K, Ursing J. The bacterial flora in the nasopharynx in healthy children. *Acta Otolaryngol (Stockh)* 1982;386 (Suppl):94-96.

55. Ekdahl K, Ahlinder I, Hansson H, et al. Duration of nasopharyngeal carriage of penicillin resistant *Streptococcus pneumoniae*: experiences from the Swedish Pneumococcal Intervention Project. *Clin Infect Dis* 1997;25:1113-1117.

56. Anderson B, Beachey E, Tomasz A, Tuomanen E, Svanborg-Eden C. A sandwich adhesion on *Streptococcus pneumoniae* attaching to human oropharyngeal epithelial cell in vitro. *Micro Pathog* 1988;4:276-278.

57. Cundell D, Gerard N, Gerard C, et al. *Streptococcus pneumoniae* anchor to activated human cells by the receptor for platelet-activating factor. *Nature* 1995;377:435-438.

58. Faden H, Duffy L, Wasieliewski R, et al. Relationship between nasopharyngeal colonisation and the development of otitis media. Tonawanda/Williamsville Pediatrics. *J Infect Dis* 1997;75:1440.

59. Mastro T, Ghafoor A, Nomani N, et al. Antimicrobial resistance of pneumococci in children with acute lower respiratory tract infection in Pakistan. *Lancet* 1991;337:156-159.

60. Lehmann D, Gratten M, Montgomery J. Susceptibility of pneumococcal carriage isolates to penicillin provides a conservative estimate of susceptibility of invasive pneumococci. *Pediatr Infect Dis J* 1997;16:297-305.

61. Hodges R, MacLeod C, Bernhard W. Epidemic pneumococcal pneumonia. III. pneumococcal carrier studies. *Am J Hyg* 1946;44:207-230.

62. Kellner J, McGeer A, Cetron MS, et al. The use of *Streptococcus pneumoniae* nasopharyngeal isolates from healthy children to predict features of invasive disease. *Pediatr Infect Dis* 1998;17:279-286.

63. Gavin PJ, Yogev R, Tan TQ. New hope for protecting a high-risk group. What you should know about the latest pneumococcal vaccine. *J Resp Dis* 2000;21:699-707.

64. Mastro T, Nomani N, Ishaq Z, et al. Use of nasopharyngeal isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae* from children in Pakistan for surveillance for antimicrobial resistance. *Pediatr Infect Dis J* 1993;12:824-830.

65. Ostroff S, Harrison L, Khaliaf N, et al. Resistance patterns of *Streptococcus pneumoniae* and *Haemophilus influenzae* isolates recovered in Egypt from children with pneumonia. *Clin Infect Dis* 1996;23:1069-1074.

66. Gehanno P, Lenoir G, Barry B, et al. Evaluation of nasopharyngeal cultures for bacteriologic assessment of acute otitis media in children. *Pediatr Infect Dis J* 1996;15:329-332.

67. Eldan M, Leibovitz E, Piglansky L, et al. Predictive value of pneumococcal nasopharyngeal cultures for the assessment of nonresponsive acute otitis media in children. *Pediatr Infect Dis J* 2000;19:298-303.

68. Butler J, Breiman R, Lipman H, Hofmann J, Facklam RR. Serotypes distribution of *Streptococcus pneumoniae* infections among preschool children in the United States, 1978-1994: implications for development of a conjugate vaccine. *J Infect Dis* 1995;171:885-889.

69. Sniadack DH, Schwartz B, Lipman H, et al. Potential interventions for the prevention of childhood pneumonia: geographic and temporal differences in

serotype and serogroup distribution of sterile site pneumococcal isolates from children - implications for vaccine strategies. *Pediatr Infect Dis J* 1995;14:503-510.

70. Kalima P, Emmanuel F, Riordan T. Epidemiology of *Streptococcus pneumoniae* infections at the Edinburgh City Hospital: 1980-95. *Epidemiol Infect* 1999;122:251-257.

71. National Advisory Committee on Immunisation. Statement on recommended use of pneumococcal conjugate vaccine. *CCDR* 2002;28:ACS-2. 1-32.

72. Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, Part I. *Clin Infect Dis* 2000;30:100-121.

73. Finland M, Barnes M. Changes in occurrence of capsular serotypes of *Streptococcus pneumoniae* at Boston City hospital during selected years between 1935 and 1974. *J Clin Microbiol* 1977;5:154-166.

74. Watson D, Musher D, Verhoef J. Pneumococcal virulence factors and host immune responses to them. *Eur J Clin Microbiol Infect Dis* 1995;14:479-490.

75. Nielsen S, Henrichsen J. Incidence of invasive pneumococcal disease and distribution of capsular types of pneumococci in Denmark, 1989-1994. *Epidemiol Infect* 1996;117:411-416.

76. Colman G, Cooke E, Cookson B, et al. Pneumococci causing invasive disease in Britain 1982-1990. *J Med Microbiol* 1998;47:17-27.

77. Sleeman K, Knox K, George R, et al. Invasive pneumococcal disease in England and Wales: vaccination implications. *J Infect Dis* 2001;183:239-246.

78. Hausdorff WP, Bryant J, Kloek C, Paradiso PR, Siber GR. The contribution of specific pneumococcal serogroups to different disease manifestations:

implications for conjugate vaccine formulation and use, part II. *Clin Infect Dis* 2000;30:122-140.

79. Obaro S, Monteil M, Henderson D. Fortnightly review: the pneumococcal problem. *BMJ* 1996;312:1521-1525.

80. Ramsey B, Mercuse E, Foy H. Use of bacterial antigen detection in the diagnosis of paediatric lower respiratory infections. *Pediatrics* 1986;78:1-9.

81. Venkatesan P, MacFarlane J. Role of pneumococcal antigen in the diagnosis of pneumococcal pneumonia. *Thorax* 1992;47:329-331.

82. Kauppinen M, Herva E, Kujala P, et al. The aetiology of community-acquired pneumonia among hospitalised patients during a *Chlamydia pneumoniae* epidemic in Finland. *J Infect Dis* 1995;172:1330-1335.

83. Porath A, Schlaeffer F, Lieberman D. The epidemiology of community-acquired pneumonia among hospitalised adults. *J Infect* 1997;34:41-48.

84. Burman L, Trollfors B, Andersson B, et al. Diagnosis of pneumonia by cultures, bacterial and viral antigens detection tests and serology with specific reference to antibodies against pneumococcal antigens. *J Infect Dis* 1991;163:1087-1093.

85. Ortqvist A. Initial investigation and treatment of the patient with severe community-acquired pneumonia. *Semi Resp Infect* 1994;9:166-179.

86. MacDonald K, Scriver S, Skuulnick M, Low D. Community-acquired pneumonia: the future of the microbiology laboratory: focused diagnosis or syndrome management. *Semi Resp Infect* 1994;9:180-188.

87. Musher DM, Mediwala R, Phan HM, Chen G, Baughn RE. Nonspecificity of assaying for IgG antibody to pneumolysin in circulating immune complexes as

a means to diagnose pneumococcal pneumonia. *Clin Infect Dis* 2001;32:534-538.

88. Greenwood B. The epidemiology of pneumococcal infection in children in the developed world. *Phil Trans R Soc Lond B* 1999;354:777-785.

89. Shann F. Aetiology of severe pneumonia in children in developing countries. *Pediatr Infect Dis J* 1986;5:247-252.

90. Shann F. Bacterial pneumonia: commoner than perceived. *Lancet* 2001;357:2070-2072.

91. Whitney CG, Schaffner W, Butler JC. Rethinking recommendations for use of pneumococcal vaccines in adults. *Clin Infect Dis* 2001;33:662-75.

92. Butler JC, Schuchat A. Epidemiology of pneumococcal infections in the elderly. *Drugs Aging* 1999;15:11-19.

93. Centres for Disease Control and Prevention. Active bacterial core surveillance (ABCs) report. Emerging infections program network: *Streptococcus pneumoniae*, 2000 (preliminary), 2001. http://www.cdc.gov/ncidod/dbmd/abcs.

94. Robinson KA, Baughman W, Rothrock G, et al. Epidemiology of invasive *Streptococcus pneumoniae* infections in the United States, 1995-1998. Opportunities for prevention in the conjugate vaccine era. *JAMA* 2001;285:1729-1735.

95. Yamanaka N, Hotomi M, Shimada J, Togawa A. Immunological deficiency in "otitis-prone" children. *Annals of New York Academy of Sciences* 1997;830:70-81.

96. Prellner K, Kalm O. Are there immuological or genetic markers that can predict recurrent acute otitis media? *Annals of the New York Academy of Science* 1997;830:82-94.

97. Teele D, Klein J, Rosner B. Epidemiology of otitis media in children. *Ann Oto Rhinol Laryngol* 1980;68 (Suppl):5-6.

98. Broome CV, Facklam RR, Austrian R, Allen J, Fraser D. Epidemiology of pneumococcal serotypes in the United States, 1978-1979. *J Infect Dis* 1980;14:119-123.

99. Burman L, Norrby R, Trollfors B. Invasive pneumococcal infections: incidence, predisposing factors and prognosis. *Rev Infect Dis* 1985;7:133-142.

100. Dagan R, Englehard D, Piccard E, et al. Epidemiology of invasive childhood pneumococcal infections in Israel. *JAMA* 1992;268:3328-3332.

101. O'Dempsey TJ, Mcardle TF, Lloyd-Evans N, et al. Pneumococcal disease among children in a rural area of West Africa. *Pediatr Infect Dis J* 1996;15:431-437.

102. Raz R, Elhanan G, Shimoni Z, et al. Pneumococcal bacteraemia in hospitalised Israeli adults: epidemiology and resistance to penicillin. *Clin Infect Dis* 1997;24:1164-1168.

103. Smith M, Stuart J, Andrews N, et al. Invasive pneumococcal infection in South and West England. *Epidemiol Infect* 1998;120:117-123.

104. Janoff E, Rubins J. Invasive pneumococcal disease in the immunocompromised host. *Microb Drug Resist* 1997;3:215-232.

105. Pastor P, Medley F, Murphy TV. Invasive pneumococcal disease in Dallas County, Texas: results from population-based surveillance in 1995. *Clin Infect Dis* 1998;26:590-595.

106. Cullingford G, Watkins D, Watts A, Mallon D. Severe late postsplenectomy infection. *Br J Surg* 1991;78:716-721.

107. Schoenmakers MCJ, Hament J, Fleer A, et al. Risk factors for invasive pneumococcal disease. *Rev Med Microb* 2002;13:29-36.

108. Stovall SH, Ainley KA, Manson EO, et al. Invasive pneumococcal infections in paediatric cardiac transplant patients. *Pediatr Infect Dis J* 2001;20:946-950.

109. Amber I, Gilbert E, Schiffman G, Jacobson J. Increased risk of pneumococcal infections in cardiac transplant recipients. *Transplantation* 1990;49:122-125.

110. Mundy L, Auwaerter P, Oldach D, et al. Community-acquired pneumonia: impact of immune status. *Am J Respir Crit Care Med* 1995;152:1309-1315.

111. Miller R, Foley N, Kessel D, Jeffrey A. Community-acquired lobar pneumonia in patients with HIV infection and AIDS. *Thorax* 1994;49:367-368.

112. Hirschtick R, Glassroth J, Jordn M, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary complications of HIV infection study group. *NEJM* 1995;333:845-851.

113. Boschini A, Smacchia C, Fine M, et al. Community-acquired pneumonia in a cohort of former injection drug users with and without human immunodeficiency virus. *Clin Infect Dis* 1996;23:107-113.

114. Schuchat A, Broome CV, Hightower A, Costa S, Parkin W. Use of surveillance data for invasive pneumococcal disease to estimate the size of the immunosuppressed HIV-infected population. *JAMA* 1991;265:3275-3279.

115. McEllistrem M, Mendelsohn A, Pass M, et al. Recurrent invasive pneumococcal disease in individuals with human immunodeficiency virus infection. *J Clin Infect Dis* 2002;185:1364-1368.

116. Rodriguez-Barradas M, Musher D, Hamill R, et al. Unusual manifestations of pneumococcal infection in human immunodeficiency virus-infected individuals: the past revised. *Clin Infect Dis* 1992;14:192-199.

117. Pesola G, Charles A. Pneumococcal bacteraemia with pneumonia: Mortality in acquired immunodeficiency syndrome. *Chest* 1992;101:150-155.

118. Garcia-Leoni M, Moreno S, Rodeno P, et al. Pneumococcal pneumonia in adult hospitalised patients infected with the human immunodeficiency virus. *Arch Intern Med* 1992;152:1808-1812.

119. Gilks CF. Acute bacterial infections and HIV disease. *Br Med Bull* 1998;54:383-393.

120. Cruciani M, Luzzati R, Fioredda F, et al. Mucosal colonisation by pyogenic bacteria among children with HIV infection. *AIDS* 1993;7:1533-1534.

121. Janoff E, O'Brein J, Thompson P, et al. *Streptococcus pneumoniae* colonisation, bacteraemia, and immune response among persons with human immunodeficiency virus infection. *J Infect Dis* 1993;167:49-56.

122. Simberkoff M, Sadr W, Schiffman G, Rahal J. *Streptococcus pneumoniae* infections and bacteraemia in patients with acquired immune deficiency syndrome, with report of a pneumococcal vaccine failure. *Am Rev Resp Dis* 1984;130:1174-1176.

123. Stover D, White D, Romano P, Gellene R, Robeson W. Spectrum of pulmonary disease associated with the acquired immune deficiency syndrome. *Am J Med* 1985;78:429-437.

124. Polsky B, Gold J, Whimbey E, et al. Bacterial pneumonia in patients with acquired immunodeficiency syndrome. *Ann Intern Med* 1986;104:38-41.

125. Redd S, Rutherford G, Sande M, et al. The role of human immunodeficiency virus infection on pneumococcal bacteraemia in San Francisco residents. *J Infect Dis* 1990;162:1012-1017.

126. Dworkin MS, Ward JW, Hanson DL, et al. Pneumococcal disease among human immunodeficiency virus-infected persons: incidence, risk factors and impact of vaccination. *Clin Infect Dis* 2001;32:794-800.

127. Hardy W, Feinberg J, Finkelstein D, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolised pentamidine for secondary prophylaxis of Pneumocystis carinii pneumonia in patients with the acquired immunodeficiency syndrome. *NEJM* 1992;327:1842-1848.

128. Vittinghoff E, Scheer S, Malley PO, et al. Combination antiretroviral therapy and recent declines in AIDS incidence and mortality. *J Infect Dis* 1999;179:717-720.

129. Nuorti JP, Butler JC, Gelling L, et al. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. *Ann Intern Med* 2000;132:182-190.

130. McIntyre P. Epidemiology and prevention of pneumococcal infections. *Curr Opin Pediatr* 1997;9:9-13.

131. Henneberger PK, Galaid EI, Marr JS. The descriptive epidemiology of pneumococcal meningitis in New York City. *Am J Epidemiol* 1983;117:484-491.

132. Harrison L, Dwyer D, Billmann L, Kolczak M, Schuchat A. Invasive pneumococcal infection in Baltimore, Md: implications for immunisation policy. *Arch Intern Med* 2000;10:89-94.

133. Nuorti J, Butler JC, Farley MM, Harrison LH, McGeer A, Kolczak MS, et al. Cigarette smoking and invasive pneumococcal disease. *NEJM* 2000;342:681-689.

134. Ammann A, Addiego J, Wara D, et al. Polyvalent pneumococcal-polysaccharide immunisation of patients with sickle-cell anaemia and patients with splenectomy. *NEJM* 1977;297:897-900.

135. Obaro SK. Prospects for pneumococcal vaccination in African children. *Acta Tropica* 2000;75:141-153.

136. Austrian R. Some observation on the pneumococcus and on the current status of pneumococcal disease and its prevention. *Rev Infect Dis* 1981;3 (Suppl):S1-S17.

137. Chen F, Breiman R, Farley M, et al. Geocoding and linking data from population-based surveillance and the US Census to evaluate the impact of median income on the epidemiology of invasive *Streptococcus pneumoniae* infections. *Am J Epidemiol* 1998;148:1212-1218.

138. MMWR. Outbreaks of pneumococcal pneumonia among unvaccinated residents in chronic care facilities --Massachusetts, October 1995, Oklahoma, Febuary, 1996, and Maryland, May-June 1996. *MMWR Morb Mortal Wkly Rep* 1997;46:60-62.

139. Fiore A, Iverson C, Messmer T, et al. Outbreak of pneumonia in a long-term care facility: antecedent human parainfluenza virus 1 infection may predispose to bacterial pneumonia. *Am J Geriatr Soc* 1998;46:1112-1117.

140. Nuorti J, Butler J, Crutcher J, et al. Outbreak of multidrug-resistant pneumococcal pneumonia and bacteraemia among unvaccinated nursing home residents. *NEJM* 1998;338:1861-1868.

141. Gleich S, Morad Y, Echague R, et al. *Streptococcus pneumoniae* serotype 4 outbreak in a home for the aged: report and review of recent outbreaks. *Infect Control Hosp Epidemiol* 2000;21:711-717.

142. MMWR. Outbreak of pneumococcal pneumonia among unvaccinated residents of a nursing home - New Jersey, April 2001. *MMWR Morb Mortal Wkly Rep* 2001;50:707-709.

143. Hoge C, Reichler M, Dominguez E, et al. Pneumococcal disease in an overcrowded inadequately ventilated jail. *NEJM* 1994;331:643-648.

144. Demaria A, Browne K, Berk S, Sherwood E, McCabe W. An outbreak of type 1 pneumococcal pneumonia in a men's shelter. *JAMA* 1980;244:1446-1449.

145. Berk S, Gage K, Holtsclaw S, Smith J. Type 8 pneumococcal pneumonia: an outbreak on an oncology ward. *South Med J* 1985;78:159-161.

146. Birch T, Levi M, Scriver S, Low D. Restriction enzyme analysis to investigate a nosocomial outbreak of penicillin-resistant *Streptococcus pneumoniae*. In: Programme and Abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy; October 17-20, 1993; New Orleans, LA, Abstract 1371.

147. Craig AS, Erwin PC, Schaaffner W, et al. Carriage of multi-resistant *Streptococcus pneumoniae* and impact of chemoprophylaxis during an outbreak of meningitis at a day care center. *Clin Infect Dis* 1999;29:1257-1264.

148. Marrie T. Community-acquired pneumonia: epidemiology, aetiology, treatment. *Infect Dis Clin Dis North Am* 1998;12:723-740.

149. Kristinsson K. Effect of antimicrobial use and other risk factors on antimicrobial resistance in pneumococci. *Micro Drug Res* 1997;3:117-123.

150. Takala A, Jero J, Kela E, et al. Risk factors for primary invasive pneumococcal disease among children in Finland. *JAMA* 1995;273:859-864.

151. Levine O, Farley M, Harrison L, et al. Risk factors for invasive pneumococcal disease in children. *Pediatrics* 1999;105:E28. http:www.pediatrics.org/cgi/content/full103/3/e28.

152. Hament JM, Kimpen JL, Fleer A, Wolfs TF. Respiratory viral infection predisposing for bacterial disease: a concise review. *FEMS Immunol Med Microbiol* 1999;26:189-195.

153. Housworth J, Langmuir A. Excess mortality from epidemic influenza, 1957-1966. *Am J Epidemiol* 1974;100:40.

154. Perrotta DM, Decker M, Glezen WP. Acute respiratory disease hospitalisations as a measure of impact of epidemic influenza. *Am J Epidemiol* 1985;122:468-476.

155. Baker W. Excess pneumonia and influenza associated hospitalisation during influenza epidemics in the United States, 1970-1978. *Am J Public Health* 1986;76:761-765.

156. Kim PE, Musher DM, Glezen WP, et al. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution and the isolation of respiratory viruses. *Clin Infect Dis* 1996;22:100-106.

157. Gray BM. *Streptococcus pneumoniae*. In: Stevens DL, Kaplan EL, editors. *Streptococcal infections. Clinical aspects, microbiology and molecular pathogenesis*: Oxford University New York, 2000:302-332.

158. Cole CL, Kanungo R, Rahmathullah L, et al. Pneumococcal nasopharyngeal colonisation in young South Indian infants. *Pediatr Infect Dis J* 2001;20:289-295.

159. Rodriguez-Barrada M, Tharapel R, Groover J, et al. Colonisation by *Streptococcus pneumoniae* among human immunodeficiency virus-infected adults: prevalence of antibiotic resistance, impact of immunization, and characterisation by polymerase chain reaction with BOX primers of isolates from persistent *Streptococcus pneumoniae* carriers. *J Infect Dis* 1997;175:590-597.

160. Afessa B, Greaves W, Frederick W. Pneumococcal bacteraemia in adults: a 14-year experience in an inner-city university hospital. *Clin Infect Dis* 1995;21:345-351.

161. Kuikka A, Syrjanen J, Renkonen OV, Valtonen V. Pneumococcal bacteraemia during a recent decade. *J Infect* 1992;24:157-168.

162. MMWR. Increase in pneumonia mortality among young adults and the HIV-epidemic- New York City, United States. *MMWR Morb Mortal Wkly Rep* 1988;37:593-6.

163. Selwyn P, Feingold A, Hartel D, et al. Increased risk of bacterial pneumonia in HIV-infected intravenous drug users without AIDS. *AIDS* 1988;2:267-272.

164. Cochi S, Fleming D, Hightower A, et al. Primary invasive *Haemophilus influenzae* type b disease. *J Pediatr* 1986;108:887-896.

165. Istre G, Conner J, Broome C, et al. Risk factors for primary invasive *Haemophilus influenzae* disease. *J Pediatr* 1985;2:190-195.

166. Takala A, Eskola J, Palmgren J, et al. Risk factors of invasive *Haemophilus influenzae* type b disease among children in Finland. *J Pediatr* 1989;115:694-701.

167. Petersen G, Silimperi D, Chiu C, et al. Effects of age, breast-feeding and household structure on *Haemophilus influenzae* type b disease risk and

antibody acquisition in Alaskan Eskimos. *Am J Epidemiol* 1991;134:1212-1221.

168. Teele D, Klein J, Rosner B. The Greater Boston Collaborative Otitis Media Programme. Beneficial effects of breast feeding on duration of middle ear effusion (MEE) after first episode of acute otitis media (AOM). *Pediat Res* 1980;14:494 (Abstract).

169. Andersson B, Porras O, Hanson L, et al. Inhibition of attachment of *Streptococcus pneumoniae* and *Haemophilus influenzae* by human milk and receptor oligosaccharides. *J Infect Dis* 1986;153:232-237.

170. Aniansson G, Andersson B, Undstedt R, et al. Anti-adhesive activity of human casein against *Streptococcus pneumoniae* and *Haemophilus influenzae*. *Microb Pathog* 1990;8:315-323.

171. O'Demsey T, McArdle T, Morris J, et al. A study of risk factors for pneumococcal disease among children in rural areas of West Africa. *Int J Epid* 1996;25:885-893.

172. Breiman RF, Spika J, Navarro V, Darden PM, Darby CP. Pneumococcal bacteraemia in Charleston County, South Carolina a decade later. *Arch Intern Med* 1990;150:1401-1405.

173. British Thoracic Society Guidelines for the Management of Community Acquired Pneumonia in Adults. Aetiology and epidemiology. *Thorax* 2001;56(Suppl IV):IV1-64.

174. Fine M, Smith M, Carson C, et al. Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. *JAMA* 1996;275:134-141.

175. Chief Medical Officer. Getting ahead of the curve. A strategy for combating infectious diseases: Department of Health, 2002.

176. Musher D. *Streptococcus pneumoniae*. In: Mandell G, Bennet J, Dolin R, editors. *Principles and practice of infectious diseases*. 4th edition: Philadelphia, Pennsylvania, Churchill Livingstone, 1994:1811-1826.

177. Dahl M, Trollfors B, Claesson B, Brandberg L, Rosengren A. Invasive pneumococcal infections in southwestern Sweden: a second follow-up period of 15 years. *Scand J Infect Dis* 2001;33:667-672.

178. von Kries R, Siedler A, Schmitt HJ, Reinert RR. Proportion of invasive pneumococcal infections in German children preventable by pneumococcal conjugate vaccines. *Clin Infect Dis* 2000;31:482-487.

179. Miller E, Waight P, Efstratiou A, et al. Epidemiology of invasive and other pneumococcal disease in children in England and Wales 1996-1998. *Acta Paediatr* 2000;435 (Suppl):11-16.

180. Kaltoft M, Zeuthen N, Konradsen H. Epidemiology of invasive pneumococcal infections in children aged 0-6 years in Denmark: a 19-year nationwide surveillance study. *Acta Paediatr* 2000;435 (Suppl):3-10.

181. Eskola J, Takala A, Kela E, et al. Epidemiology of invasive pneumococcal infections in children in Finland. *JAMA* 1992;268:3323-3327.

182. Kertesz D, Senzilet L, Alagaratnum M, et al. Invasive pneumococcal disease in Canada, 1996: results from the Sentinel Health Unit Surveillance System. *Can J Infect Dis* 1999;10 (Suppl A):22A-23A.

183. Fagan R, Hanna J, Messer R, Brookers D, Murphy D. The epidemiology of invasive pneumococcal disease in children in Far North Queensland. *J Paediatr Child Health* 2001;37:571-575.

184. Levine MM, Lagos R, Levine OS, et al. Epidemiological of invasive pneumococcal infections in infants and young children in Metropolitan

Santiago, Chile, a newly industrialising country. *Pediatr Infect Dis J* 1998;17:287-293.

185. McIntyre P, Gilmour R, Gilbert G, Kakakios A, Mellis C. Epidemiology of invasive pneumococcal disease in urban New South Wales, 1997-1999. *Med J Aust* 2000;173 (Suppl):S22-S26.

186. Voss L, Lennon D, Okesene-Gafa K, Ameratunga S, Martin D. Invasive pneumococcal disease in a paediatric population, Auckland, New Zealand. *Pediatr Infect Dis J* 1994;13:873-878.

187. Zangwill K, Vadheim C, Vannier A, et al. Epidemiology of invasive pneumococcal disease in southern California: implications for the design and conduct of a pneumococcal conjugate vaccine efficacy trial. *J Infect Dis* 1996;174:752-759.

188. Schuchat A, Robinson K, Wenger JD, et al. Bacterial meningitis in the United States in 1995. *NEJM* 1997;337:970-976.

189. Usen S, Adegbola R, Mulholland K, et al. Epidemiology of invasive pneumococcal disease in the Western region, The Gambia. *Pediatr Infect Dis J* 1998;17:23-28.

190. Bennett N, Buffington J, LaForce M. Pneumococcal bacteraemia in Monroe County, New York. *Am J Public Health* 1992;82:1513-1516.

191. Venetz I, Schopfer K, Muhlemann K. Paediatric invasive pneumococcal disease in Switzerland, 1985-1994, Swiss Pneumococcal Study Group. *Int J Epidemiol* 1998;27:1101-1104.

192. Campagne G, Garba A, Fabre P, et al. Safety and immunogenicity of three doses of a *Neisseria meningitidis* A+C diphtheria conjugate vaccine in infants from Niger. *Pediatr Infect Dis J* 2000;19:144-150.

193. Laurichesse H, Romaszko JP, Baud O, et al. Invasive pneumococcal disease: results from a population-based study in the Puy-De-Dome, France, 1994-1998. *Clin Infect Dis* 1999;29:985.

194. McKenzie H, Reid N, Dijkhuizen R. Clinical and microbiological epidemiology of *Streptococcus pneumoniae* bacteraemia. *J Med Microbiol* 2000;449:361-366.

195. Hofmann J, Cetron M, Farley M, et al. The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. *NEJM* 1995;333:481-486.

196. Mufson MA, Stanek RJ. Bacteraemic pneumococcal pneumonia in one American city: a 20-year longitudinal study, 1978-1997. *Am J Med* 1999;107 (Suppl):S34-S43.

197. Watanakunakorn C, Greifenstein A, Stroh K, et al. Pneumococcal bacteraemia in three community teaching hospitals from 1980 to 1989. *Chest* 1993;103:1152-1156.

198. Hook EI, Horton C, Schaberg D. Failure of intensive care support to influence mortality from pneumococcal bacteraemia. *JAMA* 1983;249:1055-1057.

199. Krause V, Reid S, Merianos A. Invasive pneumococcal disease in the Northern Territory of Australia, 1994-1998. *Med J Aust* 2000;173 (Suppl):S27-S31.

200. Torzillo PJ, Hanna JN, Morey F, et al. Invasive pneumococcal disease in central Australia. *Med J Aust* 1995;162:182-186.

201. Overturf GD. Technical report: prevention of pneumococcal infections, including the use of pneumococcal conjugate and polysaccharide vaccines and antibiotics prophylaxis. *Pediatrics* 2000;106:367-376.

202. Davidson M, Parkinson A, Bulkow L, et al. The epidemiology of invasive pneumococcal disease in Alaska, 1986-1990: ethnic differences and opportunities for prevention. *J Infect Dis* 1994;170:368-376.

203. Davidson M, Schraer C, Parkinson A, et al. Invasive pneumococcal disease in an Alaska native population, 1980 through 1986. *JAMA* 1989;261:715-718.

204. Cortese M, Wolff M, Almeido-Hill J, et al. High incidence rate of invasive pneumococcal disease in the White Mountain Apache population. *Arch Int Med* 1992;152:1-6.

205. Urwin G, Yuan MF, Feldman RA. Prospective study of bacterial meningitis in North East Thames Region, 1991-3, during introduction of *Haemophilus influenzae* vaccine. *BMJ* 1994;309:1412-1414.

206. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. *NEJM* 1997;336:708-716.

207. Urwin G, Yuan M, Hall L, et al. Pneumococcal meningitis in the North East Thames Region UK: epidemiology and molecular analysis of isolates. *Epidemiol Infect* 1996;117:95-102.

208. Schlech W, Ward J, Band J, et al. Bacterial meningitis in the United States. *JAMA* 1985;253:1749-1754.

209. Bohr V, Rasmussen N, Hansen B, et al. Pneumococcal meningitis: an evaluation of prognostic factors in 164 cases based on mortality and on a study of lasting sequelae. *J Infect* 1985;10:143-157.

210. Arditi M, Edward M, Bradley J, et al. Three-year multicentre surveillance of pneumococcal meningitis in children: clinical characteristics and outcome related to penicillin susceptibility and dexamethasone. *Pediatrics* 1998;102:1087-1097.

211. Bedford H, de Louvois J, Halket S, et al. Meningitis in infancy in England and Wales: follow up at age 5 years. *BMJ* 2001;323:1-5.

212. MacFarlane J. The clinical impact of pneumococcal disease. In: Mayon-White RT, ed. The clinical impact of pneumococcal disease and strategies for its prevention. *Royal Scoiety of Medicine Internation Congress and Symposium Series* 1995;210: London : Royal Society Medicine:9-17.

213. Djuretic T, Ryan M, Miller E, Fairley C, Goldblatt D. Hospital admissions in children due to pneumococcal pneumonia in England. *J Infect Dis* 1998;37:54-58.

214. MacFarlane J, Colville A, Guion A, et al. Prospective study of aetiology and outcome of adult lower respiratory tract infections in the community. *Lancet* 1993;341:511-514.

215. Bluestone C, Stephenson J, Martin L. Ten year review of otitis media pathogen. *Pediatr Infect Dis J* 1992;11(Suppl 8):S7-S11.

216. Jacobs M, Dangan R, Applebaum P, Burch D. Prevalence of antimicrobial-resistant pathogens in middle ear fluid: multinational study of 917 children with acute otitis media. *Antimicrob Agents Chemother* 1998;42:589-595.

217. Giebink GS. Otitis media: The chinchilla model. *Microb Drug Resist* 1999;5:57-72.

218. Celin S, Bluestone C, Stephenson J, Yilmaz H, Collins J. Bacteriology of acute otitis media in adults. *JAMA* 1991;266:2249-2252.

219. Brook I, Gooch WM, Reiner SA, et al. Medical management of acute bacterial sinusitis. Recommendations of a clinical advisory committee on pediatric and adult sinusitis. *Ann Otol Rhinol Laryngol* 2000;109:1-20.

220. Vernon-Feagans L. Impact of otitis media on speech, language, cognition, and behaviour. In: Rosefiled R, Bluestone C, editors. *Evidence-based otitis media.* Hamilton, Ontario: Decker, 1999:353-373.

221. Haggard M, Smith S. Impact of otitis media on child quality of life. In: Rosefiled R, Bluestone C, editors. *Evidence-based otitis media.* Hamilton, Ontario: Decker, 1999:375-398.

222. Teele D, Klein J, Chase C, et al. Otitis media in infancy and intellectual ability, school achievement, speech and language at age 7: Greater Boston Otitis Media Study Group. *J Infect Dis* 1990;162:685-694.

223. Giebink G, Juhn S, Weber M, Le C. The bacteriology and cytology of chronic otitis media with effusion. *Pediatr Infect Dis J* 1982;1:98-103.

224. Klein JO. The burden of otitis media. *Vaccine* 2001;19 (Suppl 1):S2-S8.

225. Froom J, Culpepper L, Grob P, et al. Diagnosis and antibiotic treatment of acute otitis media: report from International Primary Care Network. *BMJ* 1990;300:582-586.

226. Arason V, Kristinsson K, Sigurdsson J, et al. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? *BMJ* 1996;17:387-391.

227. Paradise J, Rockette H, Colborn E. Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. *Pediatrics* 1997;99:318-333.

228. Jacobs M. Antibiotic-resistance *Streptococcus pneumoniae* in acute otitis media: overview and update. *Pediatr Infect Dis J* 1999;17:947-952.

229. Dagan R. Treatment of acute otitis media - challenges in the era of antibiotic resistance. *Vaccine* 2001;19 (Suppl 1):S9-S16.

230. Reichler M, Allphin A, Breiman RF, at al. The spread of multiply resistant *Streptococcus pneumoniae* at a day care centre in Ohio. *J Infect Dis* 1992;166:1346-1353.

231. National Committee for Clinical Laboratory Standards (NCCLS). *Performance standards for antimicrobial susceptibility testing: 10th informational supplement. NCCLS document M100-S10*. Villanova, PA: National Committee for Clinical Laboratory Standards, 2000.

232. Klugman K. Pneumococcal resistance to antibiotics. *Clin Microbiol Rev* 1990;3:171-196.

233. Ramirez J. Penicillin-resistant pneumococci: new generation fluoroquinolones and lower respiratory tract infections. *Hosp Med* 1999;35:43-49.

234. Appelbaum P. Epidemiology and in vitro susceptibility of drug-resistant *Streptococcus pneumoniae*: an overview. *Pediatr Infect Dis J* 1996;15:932-939.

235. Johnson AP, Speller DCE, George RC, et al. Prevalence of antibiotic resistance and serotypes in pneumococci in England and Wales: results of observational surveys in 1990 and 1995. *BMJ* 1996;312:1454-1456.

236. Reacher MH, Shah A, Livermore DM, et al. Bacteraemia and antibiotic resistance of its pathogens reported in England and Wales between 1990 and 1998: trend analysis. *BMJ* 2000;320:213-216.

237. Appelbaum P. Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. *Clin Infect Dis* 1992;15:77-83.

238. Forward KR. The epidemiology of penicillin resistance in *Streptococcus pneumoniae*. *Semin Resp Infect* 1999;14:243-254.

239. Collignon PJ, Turnidge JD. Antibiotic resistance in *Streptococcus pneumoniae. MJA* 2000;173 (Suppl):S58-S64.

240. Marton A. Pneumococcal antimicrobial resistance: the problem in Hungary. *Clin Infect Dis* 1992;15:106-111.

241. Fenoll A, Jado I, Vicioso D, Perez A, Casal J. Evolution of *Streptococcus pneumoniae* serotypes antibiotic resistance in Spain: Update (1990 to 1996). *J Clin Microbiol* 1998;36:3447-3454.

242. Song JH, Lee NY, Ichiyama S, et al. Spread of drug-resistance *Streptococcus pneumoniae* in Asian countries: Asian network for surveillance of resistant pathogens (ANSORP) study. *Clin Infect Dis* 1999;28:1206-1211.

243. Doern GV, Brueggemann AB, Huynh H, Wingert E, Rhomberg P. Antimicrobial resistance with *Streptococcus pneumoniae* in the United States, 1997-98. *Emerg Infect Dis* 1999;5:757-765.

244. Jacobs MR, Felmingham D, Appelbaum PC. The Alexander Project 1998: penicillin and macrolide resistance in 2675 isolates of *Streptococcus pneumoniae* from 15 countries on five continents. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 September 1999; San Francisco, CA. Washington, DC. American Society for Microbiology, 1999:150.

245. Vaz P, Carvalho MCd, Tomasz A, et al. Antibiotic susceptibility of *Streptococcus pneumoniae* isolates in Portugal. *Microb Drug Resist* 1995;1:59-69.

246. Butler JC, Dowell SF, Breiman RF. Epidemiology of emerging pneumococcal drug resistance: implications for treatment and prevention. *Vaccine* 1998;16:1693-1697.

247. Butler JC, Cetron MS. Pneumococcal drug resistance: the new "special enemy of old age". *Clin Infect Dis* 1999;28:730-735.

248. McNeeley DF, Lyons J, Conte S, Labowitz A, Layton M. A cluster of drug resistant *Streptococcus pneumoniae* among nursing home patients. *Infect Control Hosp Epidemiology* 1998;19:476-477.

249. Reinert RR, Simic S, Al-Lahham A, et al. Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients with respiratory tract infections in Germany from 1998 to 1999: results of a national surveillance study. *J Clin Microb* 2001;39:1187-1189.

250. Overweg K, Hermans PW, Trzcinski K, et al. Multidrug-resistant *Streptococcus pneumoniae* in Poland: identification of emerging clones. *J Clin Microb* 1999;37:1739-1745.

251. Marton A, Meszer Z. Epidemiological studies on drug resistance in *Streptococcus pneumoniae* in Hungary: an update for the 1990s. *Microb Drug Resist* 1999;5:201-205.

252. Baquero F, Garcia-Rodriguez J, Garcia JLd, Aquilar L. Antimicrobial resistance of 1113 *Streptococcus pneumoniae* isolates from patients with respiratory tract infections in Spain: results from a 1-year (1996-1997) multicentre surveillance study. The Spanish Surveillance Group for Respiratory Pathogens. *Antimicrob Agents Chemother* 1999;43:357-359.

253. Zhanel G, Karlowsky J, Palatnick L, et al. Prevalence of antimicrobial resistance in respiratory tract isolates of *Streptococcus pneumoniae*: result of a Canadian national surveillance study. The Canadian Respiratory Infection Study Group. *Antimicrob Agents Chemother* 1999;43:2504-2509.

254. Jacobs M, Bajaksouzian S, Zilles A, et al. Susceptibilities of *Streptococcus pneumoniae* and *Haemophilus influenzae* to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 US surveillance study. *Antimicrob Agents Chemother* 1999;43:1901-1908.

255. Harnett N, Brown S, Riley G, Krishnan C. Penicillin resistant *Streptococcus pneumoniae* in Ontario, 1987-1995. *CCDR* 1997;1 May:23-29.

256. Castaneda E, Penuela I, Vela M, Tomasz A. Penicillin-resistant *Streptococcus pneumoniae* in Colombia: presence of international epidemic clones. Colombian pneumococcal study group. *Microb Drug Resist* 1998;4:233-239.

257. Jacobs M, Appelbaum P. Susceptibility of 1100 *Streptococcus pneumoniae* strains isolated in 1997 from seven Latin American and Caribbean countries. Laser Study Group. *Int J Antimicrob Agents* 2000;16:17-24.

258. Fabio JLD, Castaneda E, Agudelo CI, et al. Evolution of *Streptococcus pneumoniae* serotypes and penicillin susceptibility in Latin America, Sireva-Vigia Group, 1993-1999. *Pediatr Infect Dis J* 2001;20:959-267.

259. Brett W, Masters PJ, Lang SD, et al. Antibiotic susceptibility of *Streptococcus pneumoniae* in New Zealand. *N Z Med J* 1999;112:74-78.

260. Turnidge JD, Bell JM, Collignon PJ. Rapid emerging antimicrobial resistances in *Streptococcus pneumoniae* in Autralia. *MJA* 1999;170:152-155.

261. Saha S, Rikitomi N, Ruhulamin M, et al. Antimicrobial resistance and serotype distribution of *Streptococcus pneumoniae* strains causing childhood infections in Bangladesh, 1993 to 1997. *J Clin Microbiol* 1999;37:798-800.

262. Dejsirilert S, Overweg K, Sluijter M, et al. Nasopharygeal carriage of penicillin-resistant *Streptococcus pneumoniae* among children with acute respiratory

tract infection in Thailand: a molecular epidemiological study. *J Clin Microbiol* 1999;37:1832-1838.

263. Chiu S, Ho P, Chow F, Yuen K, Lau Y. Nasopharyngeal carriage of antimicrobial-resistant *Streptococcus pneumoniae* among young children attending 79 kindergartens and day care centres in Hong Kong. *Antimicrob Agents Chemother* 2001;45:2765-2770.

264. Soh S, Poh C, Lin R. Serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae* isolates from paediatric patients in Singapore. *Antimicrob Agents Chemother* 2000;44:2193-2196.

265. Hsueh P, Liu Y, Shyr J, et al. Multicentre surveillance of antimicrobial resistance of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in Taiwan during the 1998-1999 respiratory season. *Antimicrob Agents Chemother* 2000;44:1342-1345.

266. Scott J, Hall A, Hannington A, et al. Serotype distribution and prevalence of resistance to benzylpenicillin in three representative populations of *Streptococcus pneumoniae* isolates from the coast of Kenya. *Clin Infect Dis* 1998;27:1442-1450.

267. Schrag S, Beall B, Dowell S. Limiting the spread of resistant pneumococci: biological and epidemiologic evidence for the effectiveness of alternative interventions. *Clin Microbiol Rev* 2000;13:588-601.

268. Arnold K, Leggiadro R, Breiman R, et al. Risk factors for carriage of drug-resistant *Streptococcus pneumoniae* among children in Memphis, Tennessee. *J Pediatr* 1996;128:757-764.

269. Breiman R, Butler J, Tenover F, et al. Emergence of drug resistant pneumococcal infections in the United States. *JAMA* 1994;271:1831-1835.

270. Baquero F. Epidemiology and management of penicillin-resistant pneumococci. *Curr Opin Infect Dis* 1996;9:372.

271. Hermans P, Sluijter M, Dejsirilert S, et al. Molecular epidemiology of drug-resistant pneumococci: toward an international approach. *Micro Drug Resist* 1997;3:243-251.

272. Ridgway E, Allen K, Galloway A, Rigby A, Donoghue O. Penicillin-resistance pneumococci in a Merseyside hospital. *J Hosp Infect* 1991;17:15-23.

273. George R, Ball L, Cooper P. Antimicrobial-resistant pneumococci in the United Kingdom. *CDR Rev* 1992;2:R37-R43.

274. Anon. Antimicrobial resistance of pneumococci isolated from blood and cerebrospinal fluid 1993 and 1994. *CDR Rev* 1995;5:187-188.

275. Boswell T, Frodsham D, Nye K, Smith E. Antibiotic resistance and serotypes of *Streptococcus pneumoniae* at Birmingham Public Health Laboratory, 1989-1994. *J Infect* 1996;33:17-22.

276. Jacobs M, Koornhof H, Robins-Browne R, et al. Emergence of multiply resistant pneumococci. *NEJM* 1978;229:735-740.

277. Ward J, Koornhof H. Antibiotic-resistant pneumococci. In: Remington J, Swartz M, editors. *Current clinical topics in infectious diseases*. New York: McGraw-Hill Book Company, 1980:265-287.

278. Rauch A, O'Ryan M, Van R, Pickering L. Invasive disease due to multiply resistant *Streptococcus pneumoniae* in a Houston, Texas, day-care centre. *Am J Dis Child* 1990;144:923-927.

279. MMWR. Drug-resistant *Streptococcus pneumoniae* - Kentucky and Tennessee. *MMWR Morb Mortal Wkly Rep* 1993;43:23-31.

280. Baquero F. Evolving resistance patterns of *Streptococcus pneumoniae*: a link with long-acting macrolide consumption? *J Chemother* 1999;11 (Suppl 1):35-43.

281. Pradier C, Dunais B, Carsenti-Etesse H, Dellamonica P. Pneumococcal resistant patterns in Europe. *Eur J Clin Microbiol Infect Dis* 1997;16:644-647.

282. Melander E, Molstad S, Persson K, et al. Previous antibiotic consumption and other risk factors for carriage of penicillin-resistant *Streptococcus pneumoniae* in children. *Eur J Clin Microbiol Infect Dis* 1998;17:834-838.

283. Syrogiannopoulos G, Grivea I, Davies T, et al. Antimicrobial use and colonisation with erythromycin-resistant *Streptococcus pneumoniae* in Greece during the first 2 years of life. *Clin Infect Dis* 2000;31:887-893.

284. Pihlajamaki K, Kotilainen P, Kaurila T, et al. Macrolide-resistant *Streptococcus pneumoniae* and use of antimicrobial agents. *Clin Infect Dis* 2001;33:483-488.

285. Chen D, Mcgeer A, de Azavedo JC, Low D. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. Canadian Bacterial Surveillance Network. *NEJM* 1999;341:233-239.

286. Diekema D, Brueggemann A, Doern G. Antimicrobial-drug use and changes in resistance in *Streptococcus pneumoniae*. *Emerg Infect* 2000;2000:552-556.

287. Duchin J, Breiman R, Diamond A, et al. High prevalence of multi-drug resistant *Streptococcus pneumoniae* among children in a rural Kentucky community. *Pediatr Infect Dis J* 1995;14:745-750.

288. Dowell SF, Schwartz B. Resistant pneumococci: protecting patients through judicious use of antibiotics. *Am Fam Phys* 1997;55:1647-1654.

289. Nasrin D, Collingnon PJ, Roberts L, et al. Effect of β-lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study. *BMJ* 2001;323:1-4.

290. Hyde TB, Gay K, Stephens DS, et al. Macrolide resistance among invasive *Streptococcus pneumoniae* isolates. *JAMA* 2001;286:1857-1862.

291. Melnick S, Sprafka J, Laitinen D, et al. Antibiotic use in urban whites and blacks: the Minnesota Heart Survey. *Ann Pharmacother* 1992;26:1292-1295.

292. Barry AL. Antimicrobial resistant among clinical isolates of *Streptococcus pneumoniae* in North America. *Am J Med* 1999;107 (Suppl 1A):S28-S33.

293. Asensi F, Perez-Tamarit D, Otero M, et al. Imipenem-cilistatin therapy in a child with meningitis caused by a multiply resistant pneumococcus (letter). *Pediatr Infect Dis J* 1989;8:895.

294. Bradley J, Connor J. Ceftriaxone failure in meningitis caused by *Streptococcus pneumoniae* with reduced susceptibility to β-lactam antibiotics. *Pediatr Infect Dis J* 1991;10:871.

295. Leggiadro R, Barrett F, Chesney P, et al. Invasive pneumococci with use of a third generation cephalosporin resistance at a mid-south children's hospital. *Pediatr Infect Dis J* 1994;13:320.

296. John C. Treatment failure with use of a third generation cephalosporin for penicillin-resistant pneumococcal meningitis: case report and review. *Clin Infect Dis* 1994;18:188-193.

297. Pallares R, Linares J, Vasillo M, et al. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. *NEJM* 1995;333:474-480.

298. Moroney JF, Fiore AE, Harrison LH, et al. Clinical outcomes of bacteraemic pneumococcal pneumonia in the era of antibiotic resistance. *Clin Infect Dis* 2001;33:797-805.

299. Dudley M. Bacterial resistance mechanisms to β-lactam antibiotics: assessment of management strategies. *Pharmacotherapy* 1995;15 (Suppl):S9-S14.

300. Metlay JP, Hofmann J, Cetron MS, et al. Impact of penicillin susceptibility on medical outcomes for adult patients with bacteraemic pneumococcal pneumonia. *Clin Infect Dis* 2000;30:520-528.

301. Jernigan D, Cetron M, Breiman R. Minimising the impact of drug-resistant *Streptococcus pneumoniae* (DRSP): a strategy from the DRSP Working Group. *JAMA* 1996;275:206-209.

302. Guest J, Morris A. Community-acquired pneumonia: the annual cost to the National Health Service in the UK. *Eur Respir J* 1997;10:1530-1534.

303. Effective Health Care. The treatment of persistent glue ear in children. *Effective Health Care* 1992;November(4).

304. Heidelberger M, Avery O. The soluble specific substance of the pneumococcus. *J Exp Med* 1923;38:73-79.

305. Finland M, Tilghman R. Bacteriological and immunological studies of *Streptococcus pneumoniae* in infants: the development of type specific antibodies in healthy carriers. *J Clin Invest* 1936;15:501-508.

306. Musher D, Groover J, Rowland J, et al. Antibody to capsular polysaccharides of *Streptococcus pneumoniae*: prevalence, persistence and antibody response. *Clin Infect Dis* 1993;17:66-73.

307. Musher D, Groover J, Reichler M, et al. Emergence of antibody of capsular polysaccharides of *Streptococcus pneumoniae* during outbreaks of pneumonia: association with nasopharyngeal colonisation. *J Infect Dis* 1997;24:441-446.

308. Siber G. Pneumococcal disease: prospects for a new generation of vaccines. *Science* 1994;274:1385-1387.

309. Klugman KP. Efficacy of pneumococcal conjugate vaccines and their effect on carriage and antimicrobial resistance. *Lancet Infect Dis* 2001;1:85-91.

310. Simell B, Korkeila M, Pursiaenen H, Kilpi T, Kayhty M. Pneumococcal carriage and otitis media induce salivary antibodies to pneumococcal surface adhesion A, pneumolysin and pneumococcal surface protein A in children. *J Infect Dis* 2001;183:887-896.

311. Rapola J, Jantti V, Haikala R, et al. Natural development of antibodies to pneumococcal surface protein A, pneumococcal surface adhesion A and pneumolysin in relation to pneumococcal carriage and otitis media. *J Infect Dis* 2000;182:1146-1152.

312. Ambrosino D, Schiffman G, Gotschlich E, et al. Correlation between G2m(n) immunoglobulin allotype and human antibody response and susceptibility to polysaccharide encapsulated bacteria. *J Clin Invest* 1985;75:1935-1942.

313. Musher DM, Watson DA, Baughn RE. Genetic control of the immunologic response to pneumococcal capsular polysaccharides. *Vaccine* 2001;19:623-627.

314. Robbins JB, Schneerson R. Polysaccharide-protein conjugates: a new generation of vaccines. *J Infect Dis* 1990;161:821-832.

315. Robbins JB, Schneerson R, Szu SC. Perspective. Hypothesis: Serum IgG antibody is sufficient to confer protection against infectious diseases by inactivating the inoculum. *J Infect Dis* 1995;171:1387-1398.

316. Eskola J, Anttila M. Pneumococcal conjugate vaccines. *Pediatr Infect Dis J* 1999;18:543-551.

317. Eskola J, Kayhty H. Early immunisation with conjugate vaccines. *Vaccine* 1998;16:1433-1438.

318. Kayhty H, Peltola H, Karanko V, Makela P. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis* 1983;147:1100.

319. Robbins J, Austrian R, Lee C, et al. Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. *J Infect Dis* 1983;148:1136-1159.

320. Nahm M, Olander J, Magyarlaki M. Identification of cross-reactive antibodies with low opsonophagocytic activity for *Streptococcus pneumoniae*. *J Infect Dis* 1997;176:698-703.

321. Yu X, Gray B, Chang S, et al. Immunity to cross-reactive serotypes induced by pneumococcal conjugate vaccines in infants. *J Infect Dis* 1999;180:1569-1576.

322. Vakevainen M, Eklund C, Eskola J, Kayhty H. Cross-reactivity of antibodies to type 6B and 6A polysacchraides of *Streptococcus pneumoniae*, evoked by pneumococcal conjugate vaccines, in infants. *J Infect Dis* 2001;184:789-793.

323. George G. Epidemiology of pneumococcal disease. In: Mayon-White RT, ed. The clinical impact of pneumococcal disease and strategies for its prevention. *Royal Society of Medicine International Congress and Symposium Series* 1995; 210:1-5.

324. Butler J, Hofmann J, Cetron MS, et al. The continued emergence of drug-resistant *Streptococcus pneuminiae* in the United States: an update from the Centres for Disease Control and Prevention's Pneumococcal Sentinel System. *J Infect Dis* 1996;174:986-993.

325. Davis A, Aranda C, Schiffman G, Christianson L. Pneumococcal infection and immunogenic response to pneumococcal vaccine in chronic obstructive pulmonary disease: a pilot study. *Chest* 1987;92:204-212.

326. Siber G, Weitzman S, Aisenberg A, Weinstein H, Schiffman G. Impaired antibody response to pneumococcal vaccine after treatment for Hodgkin's disease. *NEJM* 1978;290:442-443.

327. Minor D, Schiffman G, McIntosh L. Response of patients with Hodgkin's disease to pneumococcal vaccine. *Ann Intern Med* 1979;90:887-892.

328. Ruben F, Uhrin M. Specific immunoglobulin-class antibody responses in the elderly before and after 14-valent pneumococcal vaccine. *J Infect Dis* 1985;151:845-848.

329. Konradsen H, Henrichsen J. Antibody response to pneumococcal vaccination in the elderly. *Int J Med Microbiol* 1991;275:94-99.

330. Romero-Steiner S, Musher DM, Cetron MS, et al. Reduction in functional antibody activity against *Streptococcus pneumoniae* in vaccinated elderly individuals highly correlates with decreased IgG antibody avidity. *Clin Infect Dis* 1999;29:281-288.

331. Douglas R, Paton J, Duncan S, Hansman D. Antibody response to pneumococcal vaccination in children younger than five years of age. *J Infect Dis* 1983;148:131-137.

332. Clemens J, Shapiro ED. Resolving the pneumococcal vaccine controversy: are there alternatives to randomised clinical trials. *Rev Infect Dis* 1984;6:589-600.

333. Fedson DS. Measuring protection: efficacy versus effectiveness. *Dev Biol Stand* 1998;195:195-201.

334. Ortqvist A. Pneumococcal vaccination: current and future issues. *Eur Respir J* 2001;18:184-195.

335. Clemes J, Brenner R, Rao M, Tafari N, Lowe C. Evaluation of new vaccines for developing countries: efficacy or effectiveness? *JAMA* 1996;275:390-397.

336. Farr B, Johnston B, Cobb D, et al. Preventing pneumococcal bacteraemia in patients at risk. Results of matched case-control study. *Arch Intern Med* 1995;155:2336-2340.

337. Peetermans WE, Lacante P. Pneumococcal vaccination by general practitioners: an evulation of current practice. *Vaccine* 1999;18:612-617.

338. Fine MJ, Smith MA, Carson CA, et al. Efficacy of pneumococcal vaccination in adults: a meta-analysis of randomised controlled trials. *Arch Intern Med* 1994;154:2666-2677.

339. Watson L. Effectiveness of pneumococcal polysaccharide vaccine: a systematic review of clinical effectiveness in adults. *Vaccine* 2002;20:2166-2173.

340. Hutchison BG, Oxman AD, Shannon HS, et al. Clinical effectiveness of pneumococcal vaccine. Meta-analysis. *Can Fam Physician* 1999;45:2381-2393.

341. Moore R, Wiffen P, Lipsky B. Are the pneumococcal polysaccharide vaccine effective? Meta-analysis of the prospective trials. *BMC Family Practice* 2000;1(1):http://biomedcentral.com/1471-2296/1/1.

342. Cornu C, Yzebe D, Leophonte P, et al. Efficacy of pneumococcal polysaccharide vaccine in immunocompetent adults: a meta-analysis. *Vaccine* 2001;19:4780-4790.

343. Bailar J. The promise and problems with meta-analysis. *NEJM* 1997;337:559-561.

344. Greenland S. A critical look at some popular meta-analytic methods. *Am J Epidemiol* 1994;140:290-296.

345. Macleod C, Hodges R, Heidelberger M, Bernhard W. Prevention of pneumococcal pneumonia by immunisation with specific capsular polysaccharides. *J Exp Med* 1945;82:445-465.

346. Austrain R, Douglas R, Schiffman G, et al. Prevention of pneumococcal pneumonia by vaccination. *Trans Assoc Am Physicians* 1976;89:184-194.

347. Smit P, Oberholzer D, Hayden-Smith S, et al. Protective efficacy of pneumococcal polysaccharide vaccines. *JAMA* 1977;238:2613-2616.

348. Riley I, Tarr P, Andrew M, et al. Immunisation with a polyvalent pneumococcal vaccine. Reduction of adult respiratory mortality in a New Guinea Highlands community. *Lancet* 1977;i:1338-1341.

349. Kaufman P. Pneumonia in old age. Active immunisation against pneumonia with pneumococcus polysaccharide: results of a six-year study. *Arch Intern Med* 1947;79:518-531.

350. Gaillat J, Zmirou D, Mallaret M, et al. Essai Clinique du vaccin antipneumococcique chez personnes agees vivant en institution. *Rev Epidemiol Sante Publique* 1985;33:437-444.

351. Simberkoff M, Cross A, Al-Ibrahim M, et al. Efficacy of pneumococcal vaccine in high-risk patients. Results of a Veterans Administrative Cooperative Study. *NEJM* 1986;315:1318-1327.

352. Ortqvist A, Hedlund J, Burman A, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in the prevention of pneumonia in middle-aged and elderly people. *Lancet* 1998;351:399-403.

353. Honkanen PO, Keistinen T, Miettinen L, et al. Incremental effectiveness of pneumococcal vaccine on simultaneously administered influenza vaccine in preventing pneumonia and pneumococcal pneumonia among persons aged 65 years or older. *Vaccine* 1999;17:2493-2500.

354. Koivula I, Sten M, Makela P. Clinical efficacy of pneumococcal vaccine in the elderly: a randomised, single-blind population-based trial. *Am J Med* 1997;103:281-290.

355. French M, Nakiyingi J, Carpenter L, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double blind, randomised and placebo controlled trial. *Lancet* 2000;355:2106-2111.

356. Christenson B, Lundbergh P, Hedlund J, Ortqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study. *Lancet* 2001;357:1008-1011.

357. Nichol KL. The addictive benefits of influenza and pneumococcal vaccinations during influenza seasons among elderly persons with chronic lung disease. *Vaccine* 1999;17 (Suppl 1):S91-S93.

358. Loeb M, McGeer A, McArthur M, Walter S, Simor AE. Risk factors for pneumonia and other lower respiratory tract infections in elderly residents of long-term care facilities. *Arch Intern Med* 1999;159:2058-2064.

359. Whitney CG. Vaccination against pneumococcal disease: current questions and future opportunities. *BioMed Central* 2000;1:7. http://www.biomedcentral.com/1471-8219/1/7.

360. Klastersky J, Mommen P, Cantraine F, Safary A. Placebo controlled pneumococcal immunisation in patients with bronchogenic carcinoma. *Eur J Cancer Clin Oncol* 1986;22:807-813.

361. Leech J, Gervais A, Ruben F. Efficacy of pneumococcal vaccine in severe chronic obstructive pulmonary disease. *CMAJ* 1987;136:361-365.

362. Forrester H, Jahnigen D, LaForce F. Inefficacy of pneumococcal vaccine in high-risk population. *Am J Med* 1987;83:425-430.

363. Butler J, Breiman R, Campbell J, et al. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. *JAMA* 1993;270:1826-1831.

364. Makela P, Leinonen M, Pukander J, Karma P. A study of the pneumococcal vaccine in prevention of clinically acute attacks of recurrent otitis media. *Rev Infect Dis* 1981;3 (Suppl):S124-S132.

365. Spika J, Fedson D, Facklam RR. Pneumococcal vaccination - controversies and opportunities. *Infect Dis Clin North Am* 1990;4:11-27.

366. Fedson D, Shapiro M, LaForce F, et al. Pneumococcal vaccine after 15 years use. Another view. *Arch Intern Med* 1994;154:2531-2535.

367. Riley I, Everingham F, Smith D, Douglas R. Immunisation with a polysaccharide pneumococcal vaccine: effect on respiratory mortality in children living in the New Guinea highlands. *Arch Dis Child* 1981;56:354-357.

368. Riely I, Lehmann D, Alpers M, et al. Pneumococcal vaccine prevents death from acute lower respiratory tract infections in Papua New Guinean children. *Lancet* 1986;ii:877-881.

369. Douglas R, Miles H. Vaccination against *Streptococcus pneumoniae* in childhood: lack of demonstrable benefit in young Austrian children. *J Infect Dis* 1984;149:861-869.

370. Douglas R, Hansman D, Miles H, et al. Pneumococcal carriage and type-specific antibody. Failure of a 14-valent vaccine to reduce carriage in healthy children. *Am J Dis Child* 1986;140:1183-1185.

371. Teele D, Klein J, Bratton L, et al. Use of pneumococcal vaccine for prevention of recurrent acute otitis media in infants in Boston. The Greater Boston Collaborative Otitis Media Study Group. *Rev Infect Dis* 1981;3 (Suppl):S113-S118.

372. Paradise J, Haggard M, Lous J, Robert J, Schilder A. Developmental implications of early-life otitis media. *Int J Pediatr Otorhinolaryngol* 1995;32(Suppl):S37-S44.

373. Sloyer J, Ploussard J, Howie V. Efficacy of pneumococcal polysaccharide vaccine in preventing acute otitis media in infants in Huntsville, Alabama. *Rev Infect Dis* 1981;3 (Suppl):S119-S123.

374. Howie V, Ploussard J, Sloyer JL, et al. Use of pneumococcal vaccine in prevention otitis media in infants: different results between racial groups. *Pediatrics* 1984;73:79-81.

375. Fiore AE, Levine OS, Elliott JA, et al. Effectiveness of pneumococcal polysaccharide vaccine for preschool-age children with chronic disease. *Emerg Infect Dis* 1999;5:828-831.

376. Fedson D, Musher D, Eskola J. Pneumococcal vaccine. In: Plotkin SA, Orenstein WA, editors. *Vaccines*. Philadelphia, Pennsylvania: W. B. Saunder Company, 1999:553-607.

377. Austrian R. Prevention of pneumococcal infection by immunisation with capsular polysaccharides of *Streptococcus pneumoniae*: current status of polyvalent vaccines. *J Infect Dis* 1977;136 (Suppl):S38-S42.

378. Broome CV, Facklam RR, Fraser D. Pneumococcal disease after pneumococcal vaccination. An alternative method to estimate the efficacy of pneumococcal vaccine. *NEJM* 1980;303:549-552.

379. Shapiro E, Clemens J. A controlled evaluation of the protective efficacy of pneumococcal vaccine for patients at high risk of serious pneumococcal infection. *Ann Intern Med* 1984;101:325-330.

380. Bolan G, Broome CV, Facklam RR, et al. Pneumococcal vaccine efficacy in selected populations in the United States. *Ann Intern Med* 1986;104:1-6.

381. Sims R, Steinmann W, McComville J, et al. The clinical effectiveness of pneumococcal vaccine in the elderly. *Ann Intern Med* 1988;108:653-657.

382. Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *NEJM* 1991;325:1453-1460.

383. Davidson M, Parkinson AJ, Bulkow LR, et al. Epidemiology of invasive pneumococcal disease: reply. *J Infect Dis* 1995;171:1065-1066.

384. Jackson LA, Benson P, Sneller VP, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. *JAMA* 1999;281:243-248.

385. Snow R, Babish J, McBean A. Is there any connection between a second pneumonia shot and hospitalisation among Medicare beneficiaries? *Public Health Report* 1995;110:720-725.

386. DeStefano F, Goodman R, Nobel G, et al. Simultaneous administration of influenza and pneumococcal vaccines. *JAMA* 1982;247:2551-2554.

387. Mosier D, Subbarao B. Thymus independent antigens: complexity of B lymphocyte activation revealed. *Immunol Today* 1982;3:217-225.

388. Stein K. Thymus-independent and thymus-dependent responses to polysaccharide antigens. *J Infect Dis* 1992;165 (Suppl):S49-S52.

389. Musher D, Luchi M, Watson D, Hamilton R, Baughan R. Pneumococcal polysaccharide vaccine in young adults and older bronchitis: determination of IgG responses by ELISA and the effect of adsorption of serum with non-type-specific cell wall polysaccharide. *J Infect Dis* 1990;161:728-735.

390. Robbins JB, Scneerson R, Anderson P, Smith DH. Prevention of systematic infections, especially meningitis, caused by *Haemophilus influenzae* type b. Impact on public health and implications for other polysaccharide-based vaccines. *JAMA* 1996;276:1181-1185.

391. Powers D, Anderson E, Lottenbach K, Mink C. Reactogenicity and immunogenicity of a protein conjugated pneumococcal oligosaccharide vaccine in older adults. *J Infect Dis* 1996;173:1014-1018.

392. Heath P, Booy R, Azzopardi H, et al. Antibody concentration and clinical protection after Hib conjugate vaccine in the United Kingdom. *JAMA* 2000;284:2334-2340.

393. Ramsay ME, Andrews N, Kaczmarski EB, Miller E. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. *Lancet* 2001;357:195-196.

394. Leinonen M, Sakkinen A, Kalliokoski R, et al. Antibody response to 14-valent pneumococcal capsular polysaccharide vaccine in pre-school age children. *Pediatr Infect Dis J* 1986;5:39-44.

395. Molrine D, George S, Tarbell N, et al. Antibody responses to polysaccharide and polysaccharide-conjugate vaccines after treatment of Hodgkin's disease. *Ann Intern Med* 1995;123:828-834.

396. Vernacchio L, Neufeld EJ, MacDonald K, et al. Combined schedule of 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal vaccine in children and young adults with sickle cell disease. *J Pediatr* 1998;133:275-278.

397. Nowak-Wegrzyn A, Winkelstein JA, Swift AJ, Lederman HM. Serum opsonic activity in infants with sickle cell disease immunised with pneumococcal polysaccharide protein conjugate vaccine. *Clin Diagn Lab Immunol* 2000;7:788-793.

398. O'Brien KL, Swift A, Winkelstein J, et al. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM(197) among infants with sickle cell disease. Pneumococcal Conjugate Vaccine Study Group. *Pediatrics* 2000;106:965-972.

399. Sorensen R, Leiva L, Giangrosso P, et al. Response to a heptavalent conjugate *Streptococcus pneumoniae* vaccine in children with recurrent infections who are unresponsive to the polysaccharide vaccine. *Pediatr Infect Dis J* 1998;17:685-691.

400. Barnett E, Pelton S, Cabral H, et al. Immune response to pneumococcal conjugate and polysaccharide vaccines in otitis-prone and otitis-free children. *Clin Infect Dis* 1999;29:191-192.

401. MMWR. Prevention and control of influenza: recommendations of the Advisory Committee on Immunisation Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2000;49 (RR03):1-38.

402. Steinhoff M. Developing and deploying pneumococcal and Haemophilus vaccines. *Lancet* 1993;342:630-631.

403. Kayhty H, Ahman H, Ronnberg PR, et al. Pneumococcal polysaccharide-meninogococcal outer membrane protein complex conjugate vaccine is immunogenic in infants. *J Infect Dis* 1995;172:1273-1278.

404. Leach A, Ceesay SJ, Banya WAS, Greenwood B. Pilot trial of a pentavalent pneumococcal polysaccharide/protein conjugate vaccine in Gambian infants. *Pediatr Infect Dis J* 1996;15:333-339.

405. Anderson E, Kennedy DJ, Geldmacher KM, et al. Immunogenicity of heptavalent pneumococcal conjugate vaccine in infants. *J Pediatrics* 1997;128:649-653.

406. Mbelle N, Huebner RE, Wasas AD, et al. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. *J Infect Dis* 1999;180:1171-1176.

407. Kayhty H, Ahman H. Bridging phase 2 and phase 3 pneumococcal immunologic data for future combination vaccine. *Clin Infect Dis* 2001;33 (Suppl):S292-S298.

408. Watson W. Pneumococcal conjugate vaccines. *Pediatr Infect Dis J* 2000;19:331-332.

409. Klein DL, Ellis RW. Conjugate vaccines against *Streptococcus pneumoniae*. In: Levine MM, Woodrow GC, Kaper JB, Cobon GS, editors. *New generation vaccines*. Second edition: New York: Marcel Dekker Inc, 1997:503-525.

410. Dagan R, Melamed R, Muallem M, et al. Reduction of nasopharyngeal carriage of pneumococci during the second year of life by a heptavalent conjugate pneumococcal vaccine. *J Infect Dis* 1996;174:1271-1278.

411. Dagan R, Melamed R, Zamir O, Leroy O. Safety and immunogenicity of tetravalent pneumococcal vaccines containing 6B, 14, 19F and 23F polysaccharide vaccines conjugated to either tetanus toxoid or diphtheria toxoid in young infants and their booster ability by native polysaccharide antigens. *Pediatr Infect Dis J* 1997;16:1053-1059.

412. Anderson E, Kenndey D, Geldmacher K, et al. Immunogenicity of heptavalent pneumococcal conjugate vaccine in infants. *J Pediatr* 1996;128:649-653.

413. Shinefield H, Black S, Ray P. Safety and immunogenicity of heptavalent pneumococcal CRM197 conjugate vaccine in infants and toddlers. *Pediatr Infect Dis J* 1999;18:757-763.

414. Zielen S, Buhring I, Strnad N, Reichenbach J, Hofmann D. Immunogenicity and tolerance of a 7-valent pneumococcal conjugate vaccine in nonresponders to the 23-valent pneumococcal vaccine. *Infect Immun* 2000;68:1435-1440.

415. Obaro S, Huo Z, Banya W, et al. A glycoprotein conjugate vaccine primes for antibody responses to a pneumococcal polysaccharide vaccine in Gambian children. *Pediatr Infect Dis J* 1997;16:1135-1140.

416. Steinhoff M, Edwards K, Keyserling H, et al. A randomised comparison of three bivalent *Streptococcus pneumoniae* glycoprotein conjugate vaccines in young children: effect of polysaccharide size and linkage characteristics. *Pediatr Infect Dis J* 1994;13:368-372.

417. Fedson D. Pneumococcal conjugate vaccination for adults: why it's important for children. *Pediatr Infect Dis J* 2000;19:183-186.

418. Ahmed F, Steinhoff M, Rodriguez-Barradas M, et al. Effect of human immunodeficiency virus type 1 on the antibody response to a glycoprotein conjugate pneumococcal vaccine: results from a randomised trial. *J Infect Dis* 1996;173:83-90.

419. Vidarsson G, Sigurdardottir S, Gudnason T, et al. Isotypes and opsonophagocytosis pneumococcus type 6B antibodies elicited in infants and adults by an experimental pneumococcus type 6B-tetanus toxoid vaccine. *Infect Immun* 1998;66:2866-2870.

420. Soininen A, Seppala I, Nieminen T, Eskola J, Kayhty H. IgG subclass distribution of antibodies after vaccination of adults with pneumococcal conjugate vaccines. *Vaccine* 1999;17:1889-1897.

421. Shelly M, Jacoby H, Riley G, et al. Comparison of pneumococcal polysaccharide vaccine and CRM 197 conjugated pneumococcal oligosaccharide vaccines in young and elderly adults. *Infect Immun* 1997;65:242-247.

422. Shelly MA, Pichichero ME, Treanor JJ. Low baseline antibody level to diphtheria is associated with poor response to conjugated pneumococcal vaccine adults. *Scand J Infect Dis* 2001;33:542-544.

423. Klugman K. Efficacy against invasive disease, pneumonia and herd immunity. 3 rd International Symposium on Pneumococci and Pneumococcal Diseases; 5-8 May, 2002; Anchorage, Alaska;2002:95.

424. O' Brien KL, Moulton L, Reid R, et al. Invasive disease efficacy of a 7-valent pneumococcal conjugate vaccine among Navajo and White Mountain apache (N/WMA) children. Society for Paediatric Research; April 2001; Baltimore, Maryland. Society for Pediatric Research; 2001; Baltimore, Maryland;2001:1371.

425. Kilpi T, Palmu A, Leinonen M, Eskola J, Finom S. Efficacy of a seven-valent pneumococcal conjugate vaccine (PncOMP) against serotype-specific otitis media (AOM) caused by *Streptococcus pneumoniae* (PNC). 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 2000; Toronto;2000:689.

426. Black S, Shinefield H, Ray P, et al. Efficacy of heptavalent conjugate vaccine pneumococcal vaccine (Wyeth Lederle) in 37,000 infants and children; results of Northern California Kaiser Permanente efficacy trial. *Pediatr Res* 1999;45:11A.

427. Dagan R. Effect of vaccine on antibiotic-resistant *Streptococcus pneumoniae* carriage and spread. International Symposium of Pneumococci and Pneumococcal Diseases; 19-23 March 2000; Sun City, South Africa,2000.

428. O'Brien KL, Moulton L, Reid RR, et al. Invasive disease efficacy of a 7-valent pneumococcal conjugate vaccine among Navajo White Mountain Apache children. *Clin Infect Dis* 2001:240A (Suppl).

429. Obaro S, Adegbola R, Banya W, Greenwood B. Carriage of pneumococci after pneumococcal vaccine. *Lancet* 1996;348:271-272.

430. O'Brien K. Pneumococcus, Hib, meningococcus disease transmission: routes, contributing factors, and herd immunity. *Int J Clin Pract* 2001;118:5-7.

431. Lipsitch M. Vaccination against colonising bacteria with multiple serotypes. *Proc Natl Acad Sci USA* 1997;94:6571-6576.

432. Lipsitch M. Bacterial vaccines and serotypes replacement: lessons from *Haemophilus influenzae* and prospects for *Streptococcus pneumoniae*. *Emerg Infect Dis* 1999;5:336-345.

433. Lipsitch M. Interpreting results from trials of pneumococcal conjugate vaccines: a statistical test for detecting vaccine-induced increases in carriage of non-vaccine serotypes. *Am J Epidemiol* 2001;154:85-92.

434. Paton J, Andrew P, Boulnois G, Mitchell T. Molecular analysis of the pathogenicity of *Streptococcus pneumoniae*: the role of pneumococcal proteins. *Annu Rev Microbiol* 1993;47:89-115.

435. Briles D, Tart RC, Swiatlo E, et al. Pneumococcal diversity: consideration for new vaccine strategies with emphasis on pneumococcal surface protein A (PspA). *Clin Microb Rev* 1998;11:645-657.

436. Briles DE, Hollingshead SK, Nabors GS, Paton JC, Brooks-Walter A. The potential for using protein vaccines to protect against otitis media caused by *Streptococcus pneumoniae*. *Vaccine* 2001;19 (Suppl 1):S87-S95.

437. Lock R, Paton J, Hansman D. Comparative efficacy of pneumococcal neuraminidase and pneumolysin as immunogens protective against *Streptococcus pneumoniae*. *Micrb Pathog* 1988;5:461-467.

438. McDaniel L, Sheffield J, Delucchi P, Briles D. PspA, a surface protein of *Streptococcus pneumoniae*, is capable of eliciting protection against pneumococci of more than one capsular type. *Infect Immun* 1991;59:222-228.

439. Paton J. Novel pneumococcal surface proteins: role in virulence and vaccine potential. *Trends Microbiol* 1998;6:85-87.

440. Briles D, Ades E, Paton J, et al. Intranasal immunisation of mice with a mixture of the pneumococcal protein PspA is highly protective against nasopharyngeal carriage of *Streptococcus pneumoniae*. *Infect Immun* 2000;68:796-800.

441. Ament A, Baltussen R, Duru G, et al. The cost effectiveness of pneumococcal vaccination for older people: a study in five western European countries. *Clin Infect Dis* 2000;31:444-450.

442. Sisk JE, Moskowitz AJ, Whang W, et al. Cost-effectiveness of vaccination against pneumococcal bacteraemia among elderly people. *JAMA* 1997;278:1333-1339.

443. Herman CM, Chen GJ, High KP. Pneumococcal penicillin resistance and the cost-effectiveness of pneumococcal vaccine. *Infect Med* 1998;15:236-243.

444. Office of Technology Assessment. A reviewe of selected Federal vaccine and immunisation policies. Washington DC: US Congress;1979.

445. Willems J, Sanders C, Riddiough M, Bell J. Cost effectiveness of vaccination against pneumococcal pneumonia. *NEJM* 1980;303:553-559.

446. Sisk J, Riegelman R. Cost-effectiveness of vaccination against pneumococcal pneumonia: an update. *Arch Intern Med* 1986;104:79-86.

447. Gable C, Holzer S, Engelhart L, et al. Pneumococcal vaccine: efficacy and associated cost savings. *JAMA* 1990;264:2910-2915.

448. Holzer S, Gable C, Friedman R. Cost effectiveness of pneumococcal vaccine: implications for managed care. *J Res Pharm Econ* 1993;5:79-95.

449. Plans PR, Garrido M, Sanmarti L. The cost effectiveness of pneumococcal vaccination in Catalonia. *Rev Esp Salud Publica* 1995;69:409-417.

450. Jimenez F, Guallar P. Cost effectiveness analysis of pneumococcal vaccination in the elderly Spanish population. *Br J Med Econ* 1996;10:193-202.

451. Baltussen R, Ament A, Leidel R, et al. Cost effectiveness of vaccination against pneumococcal pneumonia in The Netherlands. *Eur J Public Health* 1997;7:153-161.

452. Gable C, Botteman M, Savage G, Joy K. The cost effectiveness of pneumococcal vaccination strategies. *Pharmacoeconomics* 1997;12:161-174.

453. DeWals P, Guay M, Drapeau J, et al. Pneumococcal immunisation program: cost utility analysis for Quebec. *Can J Infect Dis* 1999;10 (Suppl A):46A-47A.

454. Pepper PV, Owens DK. Cost-effectiveness of the pneumococcal vaccine in the United States Navy and Marine Corps. *J Infect Dis* 2000;30:157-164.

455. Ament A, Fedson D, Christie P. Pneumococcal vaccination and pneumonia: even a low level of clinical effectiveness is highly cost-effective. *Clin Infect Dis* 2001;33:2078-9.

456. Hueston W, Mainous Ar, Brauer N. Predicting cost-benefits before programmes are started: looking at conjugate vaccine for invasive pneumococcal infections. *J Community Health* 2000;25:23-33.

457. Lieu TA, Ray GT, Black SB, et al. Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children. *JAMA* 2000;283:1460-1468.

458. Department of Health. *Immunisation against infectious disease*. London: HMSO, 1996.

459. MMWR. Influenza and pneumococcal vaccination levels among adults aged greater than or equal to 65 years -- United States, 1997. *MMWR Morb Mortal Wkly Rep* 1998;47:797-802.

460. Williams W, Hickson M, Kane M, et al. Immunisation policies and vaccine coverage among adults: the risk for missed opportunities. *Ann Intern Med* 1988;108:616-625.

461. Fedson D. Influenza and pneumococcal immunisation strategies for physicians. *Chest* 1991;3:436-443.

462. Fedson D. Adult immunisation. Summary of the National Vaccine Advisory Committee Report. *JAMA* 1994;272:1133-1137.

463. Fedson D. Influenza and pneumococcal immunisation strategies for physicians. *Chest* 1987;91:436-443.

464. MMWR. Pneumococcal immunisation programme - California, 1986-1988. *MMWR Morb Mortal Wkly Rep* 1989;38:517-519.

465. Campbell JF, Donohue M, Nevin-Woods C, et al. The Hawaii pneumococcal disease initiative. *Am J Public Health* 1993;83:1175-1176.

466. Davidson M, Chamblee C, Campbell H, et al. Pneumococcal vaccination in a remote population of high risk Alaska Natives. *Public Health Rep* 1993;108:439-446.

467. MMWR. Increasing pneumococcal vaccination rates among patients of a National Health Care Alliance - United Sates, 1993. *MMWR Morb Mortal Wkly Rep* 1995;44:741-744.

468. Chief Medical Officer (CMO). Major changes to the policy on influenza immunisation. CMO's update. 2000;26:1.

469. Nichol K. Long term success with the national health objective for influenza vaccination. *J Gen Intern Med* 1992;7:595-600.

470. Kouides R, Lewis B, Bennett NM, et al. A performance-based incentive programme for influenza immunisation in elderly. *Am J Prev Med* 1993;9:250-255.

471. Mufson M, Oley G, Hughey D. Pneumococcal disease in a medium-size community in the United States. *JAMA* 1982;248:1486.

472. Fedson D, Chairello L. Previous hospital care and pneumococcal bacteraemia: importance for pneumococcal immunisation. *Arch Intern Med* 1983;143:885-889.

473. Klein R, Adachi N. Pneumococcal vaccine in the hospital: improved use and implications for high-risk patients. *Arch Intern Med* 1983;143:1878-1881.

474. Valenti W, Magnussen C, Mushlin A. Feasibility of a vaccination programme directed at hospitalised and ambulatory patients. *Arch Intern Med* 1984;144:1755.

475. Fedson D. Hospital-based pneumococcal immunisation: the epidemiologic rationale and its implication. *Infect Control* 1982;3:303.

476. Fedson D. Improving the use of pneumococcal vaccine through a strategy of hospital-based immunisation: a review of its rationale and implications. *J Am Geriatr Soc* 1985;33:142-150.

477. Fedson D, Baldwin J. Previous hospital care as a risk factor for pneumonia: implications for immunisation with pneumococcal vaccine. *JAMA* 1982;248:1989-1995.

478. Fedson D, Kaiser D, Husted TM, et al. Hospital-based pneumococcal immunisation - epidemiologic rationale from the Shenandoah study. *Cli Res* 1984;32:221A.

479. Fedson D. Influenza and pneumococcal immunisation in medical clinics, 1971-1983. *J Infect Dis* 1984;149:817-818.

480. Klein R, Adachi N. An effective hospital-based pneumococcal immunisation programme. *Arch Intern Med* 1986;146:327-329.

481. Polis M, Smith J, Sainer D, Brenneman M, Kaslow R. Prospects for an emergency department-based adult immunisation programme. *Arch Intern Med* 1987;147:1999-2001.

482. Clancy C, Gelfman D, Poses R. A strategy to improve the utilisation of pneumococcal vaccine. *J Gen Intern Med* 1992;7:14-18.

483. Rodriguez RM, Baraff LJ. Emergency department immunisation of the elderly with pneumococcal and influenza vaccines. *Ann Emerg Med* 1993;22:93-96.

484. Gyorkos T, Tannenbaum T, Abrahamowicz M, et al. Evaluation of the effectiveness of immunization delivery methods. *Can J Public Health* 1994;85 (Suppl 1):S14-S30.

485. Smart L. Serotying of *Streptococcus pneumoniae* strains by coagglutination. *J Clin Pathol* 1986;39:328-331.

486. Information and Statistics Division (ISD). Scottish Health Statistics 1999. Scotland: ISD, 1999.

487. Berk SL, Verghese A, Berk ML, Dison C, Smith K. Survey of physician acceptance of the pneumococcal vaccine. *South Med J* 1984;77:450-454.

488. Registrar General Office (RGO). 1991 annual report. Edinburgh, Scotland: RGO, 1992.

489. Kendrick S, Clarke J. The Scottish Record Linkage System. *Health Bull (Edinb)* 1993;51:72-79.

490. Wenger J, Hightower A, Facklam RR, et al. Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. *J Infect Dis* 1990;162:1316-1323.

491. Clarke S, Reid J, Thom L, Denham B, Edwards G. Laboratory confirmation of meningococcal disease in Scotland, 1993-1999. *J Clin Pathol* 2002;55:32-36.

492. Kyaw MH, Christie P, Clarke S, et al. Invasive pneumococcal disease in Scotland in 2000: use of record linkage to explore associations between patients and disease in relation to future vaccination policy. 3rd International Symposium on Pneumococci and Pneumococcal Disease; 5-8 May 2002; Anchorage, Alaska;2002:36.

493. Rushton T, Ganguly R, Sinnott J, Banerji M. Barriers to immunisation: an examination of factors that influence the application of pneumococcal vaccine by house staff. *Vaccine* 1994;12:1173-1179.

494. Noe CA, Markson LJ. Pneumococcal vaccination: perceptions of primary care physicians. *Prev Med* 1998;27:767-772.

495. Gupta A, Morris G, Thomas P, Hasan M. Influenza vaccination coverage in old people's home in Carmarthenshire, UK, during the winter of 1998/99. *Vaccine* 2000;18:2471-2475.

496. World Health Organisation. Expert review of a tool for rapidly assessing *Haemophilus influenzae* type b (Hib) disease burden. Geneva: World Health Organisation, 2001.WHO/V&B/01.25.

497. Bryun G, van der Meer JW, Hermans J, Knoppert W. Pneumococcal bacteraemia in adults over a 10 year period at university hospital, Leiden. *Rev Infect Dis* 1988;10:446-450.

498. Sankilampi U, Herva E, Haikala R, et al. Epidemiology of invasive *Streptococcus pneumonaie* infections in adults in Finland. *Epidemiol Infect* 1997;118:7-15.

499. Ortqvist A, Klain M. Bacteraemic pneumococcal pneumonia in Stockholm, Sweden, in 1984. *Scand J Infect Dis* 1988;20:451-452.

500. Ortqvist A. Pneumococcal disease in Sweden: experiences and current situation. *Am J Med* 1999;107 (Suppl 1A):44S-49S.

501. Aszkenasy O, Geroge R, Begg N. Pneumococcal bacteraemia and meningitis in England and Wales 1982 to 1992. *CDR Rev* 1995;5:R45-R50.

502. Hedlund J, Stevenson S, Kalin M, et al. Incidence, capsular types, and antibiotic susceptibility of invasive *Streptococcus pneumoniae* in Sweden. *Clin Infect Dis* 1995;21:948-953.

503. Hausdorff W, Siber G, Paradisco P. Geographical differences in invasive pneumococcal disease rates and serotype frequency in children. *Lancet* 2001;357:950-952.

504. Lagos R, Levine L Prospective, population based surveillance for ambulatory invasive pneumococcal disease in children in Santiago, Chile. International Symposium on Pneumococcal Disease; March 2000; Sun City, South Africa;2000:26.

505. Schonheyder H, Sorensen H, Kristensen B, Korsager B. Reasons for increase in pneumococcal bacteraemia (letter). *Lancet* 1997;349:1554.

506. Kallenius G, Hedlund J, Svenson S, Kalin M, Henrichsen J. Pneumococcal bacteraemia in Sweden. *Lancet* 1997;349:1910.

507. Enright MC, Spratt BG. A multilocus sequence typing scheme for *Streptococcus pneumoniae*: identification of clones associated with serious invasive disease. *Microbiology* 1998;144:3049-3060.

508. Fiebach N, Beckett W. Prevention of respiratory infections in adults. Influenza and pneumococcal vaccines. *Arch Intern Med* 1994;154:2545-2557.

509. Hogg GG, Strachan JE, Lester RA. Invasive pneumococcal disease in the population of Victoria. *Med J Aust* 2000;173(Suppl):S32-S35.

510. Farinas-Alvarez C, Farinas M, Garcia-Palomo J, et al. Prognostic factors for pneumococcal bacteraemia in a university hospital. *Eur J Clin Microbiol Infect Dis* 2000;19:733-741.

511. Scott J, Hall A, Dagan R, et al. Serogroup-specific epidemiology of *Streptococcus pneumoniae*: associations with age, sex, and geography in 7,000 episodes of invasive disease. *Clin Infect Dis* 1996;22:973-981.

512. Roghmann KJ, Tabloski PA, Bentley DW, Schiffman G. Immune response of elderly adults to pneumococcus: variation by age, sex and functional impairment. *J Gerontol* 1987;42:265-270.

513. Roy S, Hill A, Knox K, Griffiths D, Crook D. Association of common genetic variant with susceptibility to invasive pneumococcal disease. *BMJ* 2002;324:1369.

514. Baer M, Vuento R, Vesikari T. Increase in bacteraemic pneumococcal infections in children. *Lancet* 1995;345:661.

515. Takala A, Eskola J, Leinonen M, et al. Reduction of oropharyngeal carriage of *Haemophilus influenzae* type b (Hib) in children immunised with a Hib conjugate vaccine. *J Infect Dis* 1991;164:982-986.

516. Booy R, Heath P, Willocks L, et al. Invasive pneumococcal infections in children. *Lancet* 1995;345:1245-1246.

517. Kristinsson K, Hjalmaesdottir M, Steingrimsson O. Increasing penicillin resistance in pneumococci in Iceland. *Lancet* 1992;339:1606-1607.

518. Anon. Bacteraemia and bacterial meningitis in England and Wales: 1982 to 1996. *CDR Weekly* 1997;7:275,278.

519. Anon. Notifiable diseases annual summary 1994. *CCDR* 1997;23(S9):28-30.

520. Barry M, Craven D, Finland M. Serotypes of *Streptococcus pneumoniae* isolated from blood cultures at Boston City Hospital between 1979 and 1982. *J Infect Dis* 1984;149:449-452.

521. Baraff L, Bass J, Fleisher G, et al. Practice guidelines for the management of infants and children up to 36 months of age with fever without source. *Pediatrics* 1993;92:1-12.

522. Korppi M, Koskela M, Jalonen E, Leinonen M. Serologically indicated pneumococcal respiratory infection in children. *Scand J Infect Dis* 1992;24:437-443.

523. Banya WA, O'Dempsey TJ, Mcardle T, et al. Predicators for a positive blood culture in African children with pneumonia. *Pediatr Infect Dis J* 1996;15:292-297.

524. Skerrett S. Diagnostic testing to establish a microbial cause is helpful in the management of community-acquired pneumonia. *Semin Respir Infect* 1997;12:308-321.

525. Ruiz-Gonalez A, Falguera M, Nogues A, Rubio-Caballero M. Is *Streptococcus pneumoniae* the leading cause of pneumonia of unknown aetiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. *Am J Med* 1999;106:385-390.

526. Lode H, Schaberg T, Raffenberg M, Mauch H. Diagnostic problems in lower respiratory tract infections. *J Antimicrob Chemother* 1993;32 (Suppl A):29-37.

527. Mulholland K. Strategies for the control of pneumococcal disease. *Vaccine* 1999;17 (Suppl 1):S79-S84.

528. Lim I, Shaw D, Stanley D, et al. A prospective hospital study of the aetiology of community-acquired pneumonia. *Med J Aust* 1989;151:87-91.

529. Heffron R. *Pneumonia with special reference to pneumococcal lobar pneumonia.* Cambridge, Massachusetts: Harvard University Press, 1979.

530. White B. *The biology of pneumococcus: the bacteriological, biochemical and immunological characters and activities of Diplococcus pneumoniae.* Cambridge, Massachusetts: Harvard University Press, 1979.

531. George R, Melegaro A. Invasive pneumococcal infection: England and Wales, 1999. *CDR Weekly* 2001;21 June:5-24.

532. Black S, Shinefield H, Hansen J, et al. Postlicensure evaluation of the effectiveness of 7-valent pneumococcal conjugate vaccine. *Pediatr Infect Dis J* 2001;20:1105-1107.

533. Butler J, Spika J, Nichol K, Shapiro E, Breiman RF. Effectiveness of pneumococcal vaccine. *Lancet* 1998;351:1961.

534. Boken D, Chartrand S, Goering R, et al. Colonisation with penicillin-resistant *Streptococcus pneumoniae* in a child-care centre. *Pediatr Infect Dis J* 1995;14:879-884.

535. Dowell S, Butler J, Giebink G, et al. Acute otitis media: management and surveillance in era of pneumococcal resistance - a report from the drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group. *Pediatr Infect Dis J* 1999;18:1-9.

536. Whitney CG, Farley MM, Hadler J, et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. *NEJM* 2000;343:1917-1924.

537. Lonks J, Medeiros A. High rate of erythromycin and clarithromycin resistance among *Streptococcus pneumoniae* isolates from blood cultures from Providence, Rhode Island. *Antimirob Agents Chemother* 1993;37:1742-1745.

538. Bartlett J, Breiman RF, Mandell L, File T. Community-acquired pneumonia in adults: guidelines for management. The Infectious Diseases Society of America. *Clin Infect Dis* 1998;26:811-838.

539. Cartwright K. Pneumococcal disease in Western Europe: burden of disease, antibiotic resistance and management. *Eur J Pediatr* 2002;161:188-195.

540. Soares S, Kristinsson K, Musser J, Tomasz A. Evidence for the introduction of a multiresistant clone of serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the lates 1980s. *J Infect Dis* 1993;168:158-163.

541. Doern G, Pfaller M, Kugler K, Freeman J, Jones R. Prevalence of antimicrobial resistance among respiratory tract isolates of *Streptococcus pneumoniae* in North America: 1997 results from the SENTRY antimicrobial surveillance program. *Clin Infect Dis* 1998;27:764-770.

542. Melander E, Ekdahl K, Jonsson G, Molstad S. The frequency of penicillin resistant pneumococci in children is correlated to community-level utilisation of antibiotics. *Pediatr Infect Dis J* 2000;19:1172-1177.

543. Felmingham D, Gruneberg R. The Alexander Project 1996-1997: latest susceptibility data from this international study of bacterial pathogens from community lower respiratory tract infections. *J Antimicrob Chemother* 2000;45:191-203.

544. Spanjaard L, van der Ende A, Rumke H, Dankert J, Alphen LV. Epidemiology of meningitis and bacteraemia due to *Streptococcus pneumoniae* in the Netherlands. *Acta Paediatr* 2000;435 (Suppl):22-26.

545. Molstad S, Lundborgh C, Karlsson AK, Cars O. Antibiotic prescription rates vary markedly between 13 countries. *Scand J Infect Dis* 2002;34:366-371.

546. McGee L, McDougal L, Zhou J, et al. Nomenclature of major antimicrobial-resistant clones of *Streptococcus pneumoniae* defined by the pneumococcal molecular epidemiology network. *J Clin Microb* 2001;39:2565-2571.

547. American Academic Paediatrics. *1997 red book. Report of the Committee on Infectious Diseases*. 24th ed. Elk Grove Village, ILL: American Academy of Pediatrics, 1997.

548. Heffelfinger J, Dowell S, Jorgensen J, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance. *Arch Intern Med* 2000;160:1399-1408.

549. Friedland I, Klugman K. Failure of chloramphenicol therapy in penicillin-resistant pneumococcal meningitis. *Lancet* 1992;339:405-408.

550. Poole M. Otitis media and complications and treatment failures: implications of pneumococcal resistance. *Pediatr Infect Dis J* 1995;14 (Suppl):S23-S26.

551. Quick RE, Hoge CW, Hamilton DJ, et al. Underutilisation of pneumococcal vaccine in nursing homes in Washington State: report of serotype-specific outbreak and a survey. *Am J Med* 1993;94:149-152.

552. Mehta N, Pollard A. Meningitis - bacterial meningitis. *Hosp Pharmacist* 1999;6:256-267.

553. Berg S, Trollfors B, Claesson BA, et al. Incidence and prognosis of meningitis due to *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis* in Sweden. *Scand J Infect Dis* 1996;28:247-252.

554. Rappuoli R. Conjugates and reverse vaccinology to eliminate bacterial meningitis. *Vaccine* 2000;19:2319-2322.

555. Lindberg AA. Glycoprotein conjugate vaccine. *Vaccine* 1999;17 (Suppl 2):S28-S36.

556. Schuchat A. Group B streptococcus. *Lancet* 1999;353:51-56.

557. Wenger J, Broome CV. *Bacterial meningitis: epidemiology*. In: Lambert HP, editor. *Handbook of Infectious Diseases. Infections of the nervous system*. Philadelphia, Pennsylvania: B. C. Decker Inc, 1991: 16-31.

558. Schuchat A, Wenger JD. Epidemiology of bacterial meningitis. *Annales Nestle* 1997;55:79-91.

559. Baraff L, Lee S, Schriger D. Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatr Infect Dis J* 1993;12:389-394.

560. Grimwood K, Anderson P, Anderson V, Tan L, Nolan T. Twelve year outcomes following bacterial meningitis: further evidence for persisting effects. *Arch Dis Child* 2000;83:111-116.

561. Salmaso S, Mastrantonio P, Scuderi G. Pattern of bacterial meningitis in Italy. *Eur J Epidemiol* 1997;13:317-321.

562. Molyneaux E, Walsh A, Phiri A, Molyneux A. Acute bacterial meningitis in children admitted to the Queen Elizabeth Central Hospital, Blantyre, Malawi in 1996-1997. *Trop Med Int Health* 1998;3:610-618.

563. Hargreaves RM, Slack MPE, Howard AJ, Anderson E, Ramsy ME. Changing patterns of invasive *Haemophilus influenzae* disease in England and Wales after introduction of the Hib vaccination programme. *BMJ* 1996;312:160-161.

564. Mercat A. An outbreak of pneumococcal pneumonia in two men's shelters. *Chest* 1991;99:147-151.

565. Gratten M. An outbreak of serotype 1 *Streptococcus pneumoniae* infection in central Australia. *Med J Aust* 1993;158:340-342.

566. Kalin M. Pneumococcal seotypes and their clinical relevance. *Thorax* 1998;53:159-162.

567. Cherian T, Stenhoff M, Harrison L, et al. A cluster of invasive pneumococcal disease in children in child care. *JAMA* 1994;271:695-698.

568. MMWR. Outbreak of invasive pneumococcal disease in a jail - Texas 1989. *MMWR Morb Mortal Wkly Rep* 1989;38:733-734.

569. Contempory Paediatrics. Conjugate pneumococcal vaccine: the practical issues. *Contempory Pediatrics* 2000;March:4-14.

570. Obaro S. Differences in invasive pneumococcal serotypes. *Lancet* 2001;357:1800-1801.

571. Feikin DR, Klugman KP. Historical changes in the pneumococcal serogroup distribution: implications for the era of pneumococcal conjugate vaccines. 3rd International Symposium on Pneumococci and Pneumococcal Diseases; May 5-8, 2002; Anchorage, Alaska;2002:28.

572. Smart L, Dougall A, Girdwood R. New 23-valent pneumococcal vaccine in relation to pneumococcal serotypes in systemic and non-systemic. *J Infect* 1987;14:209-215.

573. Marchese A, Tonoli E, Balistreri G, Debbia E, Schito G. Antibiotic susceptibility patterns and serotypes of antibiotic resistant and/or invasive *Streptococcus pneumoniae* strains circulating in Italy. *Microb Drug Resist* 2000;6:163-170.

574. Lovgren M, Spika JS, Talbot JA. Invasive *Streptococcus pneumoniae* infections: serotype distribution and antimicrobial resistance in Canada, 1992-1995. *CMAJ* 1998;158:327-331.

575. Jamal F. Epidemiological data on pneumococcal infections in Asian countries. *Vaccine* 1999;17 (Suppl 1):S75-S78.

576. Lee C. Bacterial capsular polysaccharide - biochemistry, immunity and vaccine. *Mol Immunol* 1987;24:1005.

577. Klugman K, Tam J. Conference report: Pneumococcal conjugate vaccines in Asia and Pacific, Singapore, 9-11 October 2000. Report of an Asia Pacific Advisory Meeting. *Vaccine* 2000;19:4579-4587.

578. Ridgway E, Tremlett C, Allen K. Capsular serotypes and antibiotic sensitivity of *Streptococcus pneumoniae* isolated from primary-school children. *J Infect* 1995;30:245-251.

579. Porat N, Trefler R, Dagan R. Persistence of two invasive *Streptococcus pneumoniae* clones of serotypes 1 and 5 in comparison to that of multiple clones of serotypes 6B and 23F among children in Southern Israel. *J Clin Microb* 2001;39:1827-1832.

580. Bradley JS. Management of community-acquired paediatric pneumonia in an era of increasing antibiotic resistance and conjugate vaccines. *Pediatr Infect Dis J* 2002;21:592-598.

581. Klein D. Development and testing of *Streptococcus pneumoniae* conjugate vaccines. In: *The Jordon Report 2000. Accelerated development of vaccines*, 2000:111-130.

582. Klein D. Pneumococcal conjugate vaccines: review and update. *Microb Drug Resist* 1995;1:49-58.

583. Butler J. Epidemiology of pneumococcal serotypes and conjugate vaccine formulations. *Microb Drug Resist* 1997;3:125-129.

584. Smith T, Lehmann D, Montogomery J, et al. Acquisition and invasiveness of different serotypes of *Streptococcus pneumoniae* in young children. *Epidemiol Infect* 1993;111:27-39.

585. Jette L, Ringuette L, Dascal A, Lapointe J. Pneumococcal resistance to antimicrobial agents in the province of Quebec, Canada. *J Clin Microbiol* 1994;32:2572-2575.

586. Beall B, McElliatrem C, Gertz R, et al. Emergence of a novel penicillin-non-susceptible, invasive serotype 35B clone of *Streptococcus pneumoniae* within the United States. *J Infect Dis* 2002;186:118-122.

587. Coffey T, Berron S, Daniels M, et al. Multiply-antibiotic-resistant *Streptococcus pneumoniae* recovered from Spanish hospitals (1988-1994): novel major clones of serotypes 14, 19F and 15F. *Microbiology* 1996;142:2747-2757.

588. Paul J, Kimari J, Gilks C. Serotypes and antibiotics susceptibilities of *Streptococcus pneumoniae* in Nairobi, Kenya. *J Infect Dis* 1996;32:139-142.

589. Gheradi G, Whitney CG, Facklam RR, Beall B. Major related sets of antibiotic resistant pneumococci in the United States based upon pulsed-field gel electrophoresis and pbp1a-pbp2b-pbp2x-dhf restriction profiles. *J Infect Dis* 2000;181:216-229.

590. McEllistrem M, Pass M, Elliott J, Whitney CG, Harrison L. Clonal groups of penicillin-nonsusceptible *Streptococcus pneumoniae* in Baltimore, Maryland: a population-based, molecular epidemiologic study. *J Clin Microbiol* 2000;38:4367-4372.

591. Spratt BG, Greenwood BM. Prevention of pneumococcal disease by vaccination: does serotype replacement matter? *Lancet* 2000;365:1210-1211.

592. Patriarca PA, Schlech WF, Hinman AR, Conn JM, Gunn WJ. Pneumococcal vaccination practices among private physicians. *Public Health Rep* 1982;97:406-408.

593. Department of Health. *Immunisation against infectious disease*. London: HMSO, 1992.

594. Irish C, Alli M, Gilham C, Joseph C, Watson J. Influenza vaccine uptake and distribution in England and Wales, July 1989-June 1997. *Health Trends* 1998;30:51-55.

595. Fedson DS, Hirota Y, Shin HK, et al. Influenza vaccination in 22 developed countries: an update to 1995. *Vaccine* 1997;15:1506-1511.

596. MMWR. Prevention and control of influenza. recommendations of the Advisory Committee on Immunisation Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2002;51:RR-3.

597. Nichol K, Baken L, Wuorenma J, Nelson A. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. *Arch Intern Med* 1999;159:2437-2442.

598. Fedson D. Pneumococcal vaccination in the prevention of community-acquired pneumonia: an optimistic view of cost-effectiveness. *Seminar Respir Infect* 1993;8:285-293.

599. Kyaw MH, Bramley JC, Chalmers J, Jones IG, Campbell H. Pneumococcal vaccination: opinion of general practitioners and hospital doctors in Scotland, 1999-2000. *Commun Dis Public Health* 2001;4:42-48.

600. Kyaw MH, Wayne B, Chalmers J, Jones I, Campbell H. Influenza and pneumococcal vaccine distribution and use in primary care and hospital settings in Scotland: coverage, practice and policies. *Epidemiol Infection* 2002;128:445-455.

601. Fedson DS, Houck P, Bratzler D. Hospital-based influenza and pneumococcal vaccination: Sutton's Law applied to prevention. *Infect Control Hosp Epidemiol* 2000;21:692-699.

602. Ratner ER, Fedson DS. Influenza and pneumococcal immunisation in medical clinics, 1978-1980. *Arch Intern Med* 1983;143:2066-2069.

603. MMWR. Adult immunization programmes in national strategies: quality standards and guidance for program evaluation and use of standing orders programs to increase adult vaccination rates. *MMWR Morb Mortal Wkly Rep* 2000;49(No.49):1-28.

604. Nichol KL. Revaccination of high-risk adults with pneumococcal polysaccharide vaccine. *JAMA* 1999;281:280-281.

605. Nicholson KG. Immunisation against influenza among people aged over 65 living at home in Leicestershire during winter 1991-2. *BMJ* 1993;306:974-6.

606. MMWR. Reasons reported by Medicare beneficiaries for not receiving influenza and pneumococcal vaccinations-- United States. *MMWR Morb Mortal Wkly Rep* 1999;48:886-890.

607. Siriwardena A. Targeting pneumococcal vaccination to high-risk groups: a feasibility study in one general practice. *Postgrad Med J* 1999;75:208-212.

608. Findlay PF, Gibbons Y, Primrose W, Ellis G, Downie G. Influenza and pneumococcal vaccination: patient perceptions. *Postgrad Med J* 2000;76:215-217.

609. Russell ML. Influenza vaccination in Alberta long-term care facilities. *CMAJ* 2001;164:1423-1427.

610. Stevenson CG, McArthur MA, Naus M, Abraham E, McGeer AJ. Prevention of influenza and pneumococcal pneumonia in Canadian long-term care facilities: how are we doing? *CMAJ* 2001;164:1413-1419.

611. Robinson C, Sepe S, Lin K. The President's Child Immunisation Initiative: a summary of the problem and the response. *Public Health Rep* 1993;108:419-425.

612. US Department of Health and Human Services. Healthy people 2010 (conference ed, in 2 vols). Washington, DC: US Department of Health and Human Services, 2000.

613. Working Party of the British Committee for Standard in Haematology Clinical Task Force. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *BMJ* 1996;312:430-434.

614. Kafidi K, Rotschafer J. Bacterial vaccines for splenectomised patients. *Drug Intell Clin Pharm* 1988;22:192-197.

615. Nicholson K, Baker D, Farquhar A, et al. Acute upper respiratory tract viral illness and influenza immunisation in homes for the elderly. *Epidemiol Infect* 1990;105:609-618.

616. Evans M, Wilkinson E. How complete is influenza vaccination coverage? A study in 75 nursing and residential home for the elderly people. *Br J Clin Pract* 1995;45:419-421.

617. Evans M. Monitoring influenza immunisation uptake in nursing homes. *CDR Rev* 1996;6:R170, R172.

618. Kelly T, Dillaard J, Yother J. Effect of genetic switching of capsular type on virulence of *Streptococcus pneumoniae*. *Infect Immun* 1994;62:1813-1819.

APPENDICES

a. Ethical approval and co-operation

b. Random sample selection method for surveys 1 and 2

c. Survey 1 questionnaire

d. Survey 2 questionnaire

e. Survey 3 questionnaire

f. Survey 4 questionnaire

g. Summary of record linkage study results

h. Glossary

i. List of studies conducted by author at SCIEH

j. Copy of published articles by author related to this thesis

a. Ethical approval and co-operation

isd Scotland NATIONAL HEALTH SERVICE IN SCOTLAND

Information & Statistics Division

Trinity Park House
South Trinity Road
Edinburgh EH5 3SQ

Tel: (0131) 552 6255 ext. 2843
+44 131 552 6255 (international)
GTN: 7167
FAX: (0131) 551 1392 (UK)
+44 131 551 1392 (international)

Mr MH Kyaw
Research Student
SCIEH
Clifton House
Clifton Place
GLASGOW
G3 7LN

Your Reference

Our Reference MB/IS

Date 11 February 2000

Dear Mr Kyaw

VACCINATION STATUS IN ASPLENIC INDIVIDUALS: AN AUDIT OF PNEUMOCOCCAL, HAEMOPHILLUS INFLUENZAE AND NEISSERIA MENINGITIS VACCINE UPTAKE IN SCOTLAND

Thank you for your letter of 7 February 2000 in which you clarified the issues raised by the Privacy Advisory Committee. I can confirm that the data you requested can now be released to you. As you require details of those who have died we will provide the information using the linked SMR01 to GROS deaths dataset. A member of the Record Linkage Team will be in touch with you in the near future.

Yours sincerely

Dr Marion Bain
Consultant in Public Health Medicine

c.c. James Boyd, Record Linkage Team

ARGYLL AND CLYDE HEALTH BOARD
ACTION HEALTH

Direct Line: 0141-842-7207
Direct Fax: 0141-848-0165

E mail: lewis.reay@achb.scot.nhs.uk

Your Ref:
Our Ref: lmr/lmci/
Date: 30 November 1999

Dr I Jones
Director
Scottish Centre for Infection & Environmental Health
Clifton House
Clifton Place
Glasgow G3 7LN

Dear ~~Dr Jones~~ Tom

PNEUMOCOCCAL DISEASE AND ASPLENIC PATIENTS

I write to confirm permission for access to Argyll and Clyde residents for the project on pneumococcal disease in Scotland as described in your letter of 27 October 1999.

I hope the audit goes well and we look forward to learn of the findings in due course.

Kind regards.

Yours sincerely

Lewis M Reay
DEPUTY DIRECTOR OF PUBLIC HEALTH

AYRSHIRE AND ARRAN
HEALTH BOARD

HEAD OFFICE
Boswell House
10 Arthur Street
AYR KA7 1QJ

Tel: (01292) 611040
Fax: (01292) 885890

Our Ref: OW001/MKC Your Ref: If phoning, please ask for: 01292 885882

18 November 1999

Dr Ian Jones
Director
Scottish Centre for Infection and Environmental Health
Clifton House
Clifton Place
GLASGOW G3 7LN

Dear Ian

HAEMOPHILUS INFLUENZAE AND NEISSERIA MENINGITIS VACCINE UPTAKES AMONG ASPLENIC INDIVIDUALS IN SCOTLAND

Thank you for your letter of 27 October regarding the above which I received on 10 November. I confirm that I am in agreement to your accessing details of asplenic Ayrshire and Arran patients registered at ISD during the period 1998 – 1998/99. The release of this data is on the understanding that it will be used solely for the purposes outlined in your letter.

Kind regards.

Yours sincerely

Drew Walker
Director of Public Health

SHETLAND HEALTH BOARD

Dr Ian Jones
SCIEH
Clifton House
Clifton Place
Glasgow
G3 7LN

11 November, 1999

Dear Ian

Thanks for your letter of 27th October, which arrived in Shetland on 10th November. I am happy that ISD should release details of asplenic Shetlanders to you.

Yours sincerely,

Dr Norman Waugh
ACTING DIRECTOR OF PUBLIC HEALTH

BOARD HEADQUARTERS, Brevik House, Lerwick, Shetland ZE1 0TG
Telephone (01595) 696767 Fax: (01595) 696727

HIGHLAND
HEALTH BOARD
WORKING TO IMPROVE HEALTH

Department of Public Health

Tel No: (01463) 704886 Direct Dial
Fax No: (01463) 717666
e-mail: reception@ms.highland-hb.scot.nhs.uk

Your Ref:
Our Ref: KO/IMcK

12 November 1999

Dr Ian Jones
Director
SCIEH
Clifton House
Clifton Place
GLASGOW
G3 7LN

Dear Ian

AUDIT OF ASPLENIC PATIENTS

I am happy to give permission for details of all asplenic patients resident in Highland to be released from ISD to yourselves for the purposes of the audit project you outlined in your recent letter of 27 October.

I look forward to seeing the findings of this.

Yours sincerely

Dr Ken Oates
Consultant in Public Health Medicine

19/11 —> Moe

Grampian Health Board

Grampian Health Board
Summerfield House
2 Eday Road
Aberdeen AB15 6RE
Tel: (01224) 663456
Fax: (01224) 404014

If telephoning please ask for Ext 75203

Dr Ian Jones
Director
SCIEH
Clifton House
Clifton Place
GLASGOW, G3 7LN

Your ref

Our ref HH/NW/KS/Jones.let

Date 7 September, 1999

Dear Dr Jones

Vaccination Status in Asplenic Individuals: An Audit of Hospital and Primary Care Aspienic Register Database in Scotland

We have recently been contacted by Moe Hein Kyaw, a Research Student at SCIEH, who has written on your behalf requesting the Health Board to release named patient data to SCIEH to facilitate an audit of vaccination status. I enclose copies of the correspondence.

Grampian Health Board currently holds a register of asplenic patients and I would be happy to release anonymised data from the register, but this would not provide all the data requested by SCIEH. The register currently holds no information on the hyposplenic population in Grampian. It would not be able to provide detailed information on reason for splenectomy nor whether it was performed as an elective or emergency procedure. Although some information is held on the use of antibiotic prophylaxis, we do not know the current status of individual patients. Additionally no detailed information is held on pneumococcal or other infections in this group of patients.

Following consideration of this request, I confirm the Health Board is prepared to release patient and GP details to allow SCIEH to contact the GP to request data for the audit. However in order to comply with best practice, the data will only be released on the following basis:

- It is to be used **only for the purpose stated in the letter**, i.e. to allow audit of compliance with current guidelines issued by the Department of Health and British Committee for Standards in Haematology for the specific purpose of informing the planning of future service provision

- The data will be released into the care of the Caldicot guardian of SCIEH (yourself)

If you find these terms acceptable, please confirm this in writing and I will then arrange for the data to be released into your care.

Yours sincerely

Dr Norman Waugh
Acting Director of Public Health

cc. Moe Hein Kyaw, SCIEH
Anne-Marie Noble, Health Information Developer/Data Protection, GHB
Stephen Conaty, Locum Consultant in Public Health Medicine, GHB
Helen Howie, Senior Registrar in Public Health Medicine, GHB

GREATER GLASGOW
HEALTH BOARD

Your Ref:
Our Ref: HB/JMM
Contact: Dr H Burns
Direct Line: 0141-201 4602
Fax: 0141-201 4601

30 November 1999

Dr I Jones
Director
Scottish Centre for Infection and Environmental Health
Clifton House
Clifton Place
GLASGOW
G3 7LN

Dear Ian

ASPLENIC PATIENT STUDY

Thank you for your note. I am happy to agree to the release of details of asplenic patients from the Greater Glasgow Health Board area registered at ISD from 1988 to 1999.

Kind regards.

Yours sincerely

DR H BURNS
Director of Public Health

POSITIVE ABOUT DISABLED PEOPLE

FORTH VALLEY HEALTH BOARD

AJH/ksh/0480

15th December 1999

Dr Ian Jones
Director
Scottish Centre for Infection and Environmental Health
Clifton House
Clifton Place
GLASGOW
G3 7LN

Dear Dr Jones

RE: Vaccination Status in Asplenic Individuals: an Audit of Pneumococcal, Haemophilus Influenzae and Neisseria Meningitidis Vaccine Uptake in Scotland

I refer to your letter of 27th October, which Dr McWhirter, Director of Public Health passed on to the Forth Valley Ethics of Research Committee and which was discussed by that Committee on 9 December 1999.

The Committee agreed that this is an audit exercise and that a full submission for ethical approval is not required.

Yours sincerely

Dr A J Holliday
Secretary to Ethics of Research Committee

c.c. Dr M McWhirter

33 Spittal Street, Stirling, FK8 1DX
Telephone: 01786 -457251
Facsimile: 01786 - 451474

FIFE HEALTH BOARD

Springfield House
Cupar
Fife
KY15 5UP

Tel: (01334) 656200
Fax: (01334) 652210
Text: 0345 626799

Your Ref:
Our Ref: LM/JB/LM070
Enquiries to: Dr L Macdonald
Ext: Dir. Line 01334 421111
Dept Fax: 01334 657579
E-Mail:

12 January 2000

Dr I G Jones
Director
Scottish Centre for Infection & Environmental Health
Clifton House
Clifton Place
GLASGOW
G3 7LN

Dear ~~Dr Jones~~ Ian

AUDIT OF VACCINE UPTAKES AMONG ASPLENIC INDIVIDUALS IN SCOTLAND

I have now discussed this proposed audit with the Chairman of our Local Ethics Committee who considers that the proposal does not require to be submitted for ethical approval. I understand that Dr Jim Chalmers, Information & Statistics Division, can provide the details of asplenic patients registered at ISD from 1988-1998/9. I am happy that he releases the relevant information to you.

Kind regards.

Yours sincerely

I apologise for the delay in responding.

DR LESLEY MACDONALD
Director of Public Health

DUMFRIES and GALLOWAY HEALTH BOARD

GRIERSON HOUSE, THE CRICHTON,
BANKEND ROAD, DUMFRIES. DG1 4ZG

Tel: Dumfries (01387) 272700
Fax: 01387 252375

DEPARTMENT OF PUBLIC HEALTH MEDICINE

ur Ref. **DC/JS** Your Ref.

Enquiries to:
Direct Dial (01387) 272725
Confidential Fax: (01398) 272759
Internal Ext. 32725

01 December 1999

Dr. Ian Jones
Director
SCIEH
Clifton House
Clifton Place
GLASGOW G3 7LN

Dear Dr. Jones

Vaccine Uptake in Asplenic Patients

I hereby authorise ISD to provide you with details of asplenic patients registered in Dumfries and Galloway from 1988 onwards.

Yours sincerely,

DR DEREK COX
Director of Public Health

BORDERS
HEALTH

Borders Health Board

Department of Public Health
Newstead
Melrose
Roxburghshire
TD6 9DB

Tel Direct Dial: 01896 82 5560
Fax : 01896 82 5580
e-mail: bordershb@compuserve.com

Your Ref :
Our Ref : AR/SMP

19 November 1999

Dr Ian Jones
Director
Scottish Centre for Infection and Environmental Health
Clifton House
Clifton Place
GLASGOW G3 7LN

Dear Ian

AUDIT OF PNEUMOCOCCAL, HAEMOPHILUS INFLUENZA AND NEISSERIA MENINGITIDIS VACCINE UPTAKES AMONG ASPLENIC INDIVIDUALS IN SCOTLAND

Thank you for your letter of 27 October 1999 about this audit proposal where you have requested written permission from me for release of asplenic patient details to SCIEH.

Please accept this letter as permission for I.S.D. to release such patient details to you. I look forward to seeing a full copy of the result after the completion of this audit.

If you require any further details or clarification please do not hesitate to contact me.

Kind regards,

Yours sincerely

Dr A Riley
Director of Public Health
Chief Administrative Medical Officer

Bòrd Slàinte nan Eilean Siar

Western Isles Health Board

Ar Faidhle:
Our Ref:

Ur Faidhle:
Your Ref:

Stiùiriche Slàinte Phoblach

22nd November 1999

Dr Ian Jones,
Director,
Scottish Centre for Infection & En. Health,
Clifton House,
Clifton Place,
Glasgow, G3 7LN

Dear Dr Jones,

Vaccination Status in Asplenic Individuals

Thank you for your letter of 27th October on this subject.

I am content for you to be sent the names of asplenic patients in the Western Isles for the purpose of this study.It seems a very interesting project and will act as an *aide-memoire* for general practitioners so that any patients who have slipped through the net will then be vaccinated.

You may be interested to know that we are funding a special programme this winter by paying general practitioners to vaccinate as many as possible in the "at-risk" groups against influenza and pneumococcus.

With kind regards,
Yours sincerely,

A.M.George,
Director of Public Health/CAMO

Dr. A. Michael George
Director of Public Health
Health Board Offices, 37 South Beach Street,
Stornoway, Isle of Lewis HS1 2BB
Tel: 01851 702997 Fax: 01851 706720
E-mail: wihb@sol.co.uk

Dr. A. Michael MacDheòrsa
Stiùiriche Slàinte Phoblach
Oifisean Bòrd na Slàinte, 37 Mol a Deas,
Steòrnabhagh, Eilean Leodhais HS1 2BB
Fòn: 01851 702997 Facs: 01851 706720
Post Dealain: wihb@sol.co.uk

b. Random sample selection method for surveys 1 and 2

The SPSS statistical package was used for random sample selection in these surveys. A detailed method, SPSS random select function, is described below.

SPSS random select function

This function allows selecting a random sample based on an exact number of cases.

1. Specify a user-specific number of cases.

2. Specify the number of cases from which to generate the sample. This second number should be less than or equal to the total number of cases in the data file. If the number exceeds the total number of cases in the data file, the sample will contain proportionally fewer cases than requested number.

3. Syntax.

4. Sample requested from the total number of cases.

Example: the selection of 10 patients from every CMR practice in survey 2

Create an SPSS file for each CMR practice, containing a record for every patient with one or more of the specified conditions/illnesses.

Use SPSS aggregated function to count the number of these patients in each practice (eg. Practice 1 had 466 patients, Practice 2 had 155 patients etc.).

Open File A and selected only patients in Practice 1

Use SPSS random select function (as stated above) to randomly select 10 patients from all 466 patients.

c. Survey 1 questionnaire

Pneumococcal polysaccharide vaccine has been available for use since 1979. However, the usage of this vaccine remains low among recommended individuals and the reasons are poorly understood. This survey is to identify the relevant factors which may affect the use and administration of pneumococcal vaccine in primary and hospital care.

Adult pneumococcal polysaccharide immunisation: a survey of general practitioners'/ hospital doctors' knowledge, attitudes and practices towards pneumococcal polysaccharide vaccine

(Please tick as appropriate)

	Strongly Agree	Agree	Disagree	Strongly Disagree	Don't Know
1. The vaccine should be targeted to patients with:					
a. chronic pulmonary disease	❐	❐	❐	❐	❐
b. chronic heart disease	❐	❐	❐	❐	❐
c. chronic renal disease	❐	❐	❐	❐	❐
d. chronic liver disease	❐	❐	❐	❐	❐
e. immunodeficiency & immuno suppression	❐	❐	❐	❐	❐
f. Diabetes mellitus	❐	❐	❐	❐	❐
g. asplenia & severe splenic dysfunction	❐	❐	❐	❐	❐
h. all older people aged ≥65 years	❐	❐	❐	❐	❐
i. all older people (≥65 years) who are residents of long stay facilities	❐	❐	❐	❐	❐

j. others (please specify): ______________________________

____

	Strongly Agree	Agree	Disagree	Strongly Disagree	Don't Know
2. The vaccine has proven safe and effective in preventing invasivepneumococcal disease in:					
a. young adults	❐	❐	❐	❐	❐
b. older people (≥65 years)	❐	❐	❐	❐	❐
c. adults with chronic heart/ pulmonary/renal/liver disease	❐	❐	❐	❐	❐
d. immunosuppressed adults	❐	❐	❐	❐	❐

3. Last year, I have used the pneumococcal vaccine:

Not at all	❐	(30-49) times	❐
(0-9) times	❐	(50-99) times	❐
(10-29) times	❐	≥ 100 times	❐

4. For an elderly patient, who requests a vaccine against pneumonia, I would give:

Pneumococcal vaccine	❐
Influenza vaccine	❐
Both	❐
Neither	❐

Others (please comment): ______________________________

PTO for Q.5/....

5. Pneumococcal immunisation policies in my practice/hospital include:

- Written policies with target ☐
- Written policies without target ☐
- Verbal agreement on use among partners ☐
- No policy ☐

Others (please specify): ____________________

6. If the vaccine is proven effective and safe, the primary responsibility for its use should lie with: **(please tick more than one if necessary)**

- The patients ☐
- Hospital physicians ☐
- General practitioners ☐
- Health Boards ☐
- The Department of Health ☐

Others (please specify): ____________________

7. My knowledge of pneumococcal vaccine comes from: **(please tick more than one if necessary)**

- Own review of medical literature ☐
- Discussion with colleagues ☐
- Further medical education ☐
- Advice of manufacturer ☐
- Past experience ☐
- The Department of Health ☐
- Local Health Board guidelines ☐

Others (please specify): ____________________

8. Which of the following do you think would help to improve pneumococcal vaccine coverage in in primary care? **(please tick more than one if necessary)**

- A clear immunisation policy ☐
- Financial support for vaccinations ☐
- Further education on immunisation ☐
- Nurse assistant ☐
- Computerised systems to identify high risk patients ☐
- Conclusive evidence of vaccine efficacy ☐
- Vaccine awareness public health campaign ☐

Others (please specify): ____________________

d. Survey 2 questionnaire

SCIEH

Survey of influenza and pneumococcal vaccine uptake in the CMR practices, Scotland

General Practice Location: ....

General Practitioner: ....

Please tick as appropriate for the each patient's *vaccine status* and *place of vaccination*.

Patient number	Search information		Pneumococcal vaccine: Vaccine status		Pneumococcal vaccine: Place of vaccination		Influenza vaccine: Vaccine status		Influenza vaccine: Place of vaccination	
1.	D.O.B. Sex Post code		Yes	No	General practice	Hospital	Yes	No	General practice	Hospital
2.	D.O.B. Sex Post code		Yes	No	General practice	Hospital	Yes	No	General practice	Hospital
3.	D.O.B. Sex Post code		Yes	No	General practice	Hospital	Yes	No	General practice	Hospital
4.	D.O.B. Sex Post code		Yes	No	General practice	Hospital	Yes	No	General practice	Hospital
5.	D.O.B. Sex Post code		Yes	No	General practice	Hospital	Yes	No	General practice	Hospital
6.	D.O.B. Sex Post code		Yes	No	General practice	Hospital	Yes	No	General practice	Hospital
7.	D.O.B. Sex Post code		Yes	No	General practice	Hospital	Yes	No	General practice	Hospital
8.	D.O.B. Sex Post code		Yes	No	General practice	Hospital	Yes	No	General practice	Hospital
9.	D.O.B. Sex Post code		Yes	No	General practice	Hospital	Yes	No	General practice	Hospital
10.	D.O.B. Sex Post code		Yes	No	General practice	Hospital	Yes	No	General practice	Hospital

Vaccine should be targeted to patients with (please tick as appropriate):

High-risk conditions	Pneumococcal vaccine	Influenza vaccine
Chronic pulmonary disease		
Chronic heart disease		
Chronic renal disease		
Chronic liver disease		
Immunodeficiency & immunosuppression		
Diabetes mellitus		
Splenic disorders		
All elderly ≥65years of age		
Long stay care elderly residents >65 years of age		
Others (please specify)		

Immunisation policies in my practice include (please tick as appropriate):

Policy	Pneumococcal vaccine	Influenza vaccine
Written policies with target		
Written policies without target		
Verbal agreement on use among partners		
No policy		
Others (please specify)		

If the vaccine is proven effective and safe, the primary responsibility for its use should lie with: ***(please tick more than one if necessary)***

Category	Pneumococcal vaccine	Influenza vaccine
The patient		
Hospital physicians		
General practitioners		
Health Boards		
The Department of Health		
Others (please specify)		

e. Survey 3 questionnaire

Survey of Influenza and Pneumococcal Vaccination in Nursing Homes

Questionnaire

- The number of general practices looking after residents ☐
- The number of residents ☐
- The existence of systematic immunisation cards (not medical or nursing records) **Yes** ☐ **No** ☐
- The number vaccinated: -
  Influenza vaccine (2000-01) ☐
  Pneumococcal vaccine within last 5 years ☐
  Both vaccines ☐

- **Factors which could improve coverage of both vaccines** *(tick all that apply)*

Factors	Influenza and pneumococcal vaccine
A clear vaccination policy	
Payment for vaccine	
Active promotion of vaccine	
Improved immunisation records	
Vaccine programme organised by nursing staff	
Need to review vaccination status of residents yearly	
Awareness and education for both staff and residents	
Consent on behalf of the incompetent residents	
Others (please specify)	

- **Policies for vaccination** *(tick all that apply)*

Policies	Influenza vaccine	Pneumococcal vaccine	Both vaccine
Written policies with set target			
Written policies without set target			
Verbal agreement among partners			
No policy			
Others (please specify)			

- **Main reasons for receipt of vaccines** *(tick all that apply)*

Reasons	Influenza	Pneumococcal
Advice from community doctor & nurse		
Advice from hospital doctor & nurse		
Advice from friends & family		
Leaflets/posters		
Media (radio and TV)		
Policies & guidelines at nursing home		
Vaccine provides protection against respiratory infection		
Others (please specify)		

- **Main reasons for non-receipt of vaccines** *(tick all that apply)*

Reasons	Influenza	Pneumococcal
GPs not recommended		
Refused by resident		
Refused by family member		
Never heard of it		
Side effects		
Contraindications		
Vaccine is not effective		
Refused vaccine (no reason given)		
Others (please specify)		

SCIEH

f. Survey 4 questionnaire

SPLENECTOMY IMMUNISATION

SCIEH

PLEASE CIRCLE THE RELEVANT ANSWERS

Is the patient currently on your list? YES NO

If "yes" has this patient had a splenectomy? YES NO

Please fill in the rest of the form only if this patient is on your list and has had a splenectomy (or) hyposplenic condition.

What was the date of the operation? ____/____/____

What was the reason for the splenectomy? ________________________

Was it performed as an elective or emergency procedure? ELECTIVE EMERGENCY

What were the other underlying medical conditions that lead to the splenectomy (if present) ________________________

Is this patient vaccinated against: -	*Streptococcus pneumoniae*	*Haemophilus influenzae type B*	*Neisseria meningitidis*	*Influenza*
	YES NO Don't know	YES NO Don't know	YES NO Don't know	YES NO Don't know
If "Yes", was the patient vaccinated prior to operation?	YES NO Don't know	YES NO Don't know	YES NO Don't know	YES NO Don't know
What was the date of the most recent vaccination?	__/__/__	__/__/__	__/__/__	__/__/__

Does this patient take long-term prophylaxis with an antibiotic? YES NO

Has this patient been admitted to hospital for any infection since developing asplenia? YES NO

PLEASE RETURN THE ORIGINAL QUESTIONNAIRE and NOT A PHOTOCOPY

Scottish Centre for Infection & Environmental Health, Clifton House, Clifton Place, Glasgow, G3 7LN

g. Summary of record linkage study results

Scottish Centre for Infection
and Environmental Health
Clifton House, Clifton Place, Glasgow G3 7LN
Tel: 0141 300 1100 Fax: 0141 300 1170

NHS SCOTLAND

Invasive pneumococcal disease in Scotland in 2000: use of record linkage to explore associations between patients and disease in relation to future vaccination policy

Moe H Kyaw[1,2], Peter Christie[1], Stuart Clarke[3], Jim Chalmers[4], Ian G Jones[1], Harry Campbell[2]

Background

- The pneumococcus is an important cause of death and hospitalisation in Scotland, and incurs large health care costs.
- A 7-valent pneumococcal conjugate vaccine has gained licensure in the UK and is expected to be considered for the routine childhood immunisation schedule.
- The vaccine only covers most of the more common serotypes, but may have to be tailored for specific age groups and geographical locations.
- Knowledge of local disease epidemiology can provide important strategic data for deciding appropriate vaccination polices and other preventive interventions.

Methods

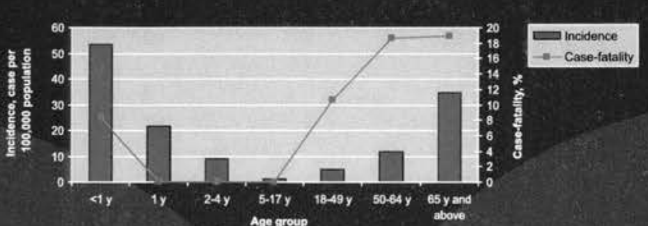
- Enhanced pneumococcal surveillance was established in November 1999 in Scotland, in a collaboration between SCIEH and SMPRL.
- Isolates submitted to SMPRL were confirmed as pneumococci by antigen testing. Coagglutination testing was used for serogrouping/typing and the E-test method for antibiotic susceptibility.
- Data on cases of invasive pneumococcal disease (IPD) reported to SCIEH and to SMPRL in 2000 were linked to Scottish hospital discharge records (SMR01) and to death certificate data recorded by the General Register Office in Scotland (GRO).
- Record linkage was carried by probability matching using date of birth, sex, name and other identifiers.
- This methodology will provide an ongoing active system for monitoring of any future effects of vaccination on the epidemiological features of IPD.

Results

559 cases of IPD recorded in 2000. 348 (62.2%) were successfully linked to SMR01 and GRO records. 364 (65.1%) were serogrouped. Antibiotic susceptibility was measured in 350 cases (62.6%) for penicillin, 357 (63.9%) for erythromycin and 348 (62.3%) for ciprofloxacin.

Graph 1.

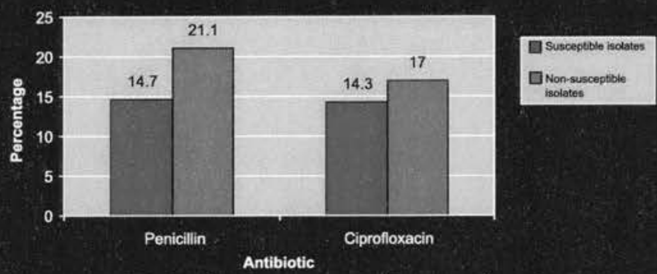
Incidence and case-fatality rate of invasive pneumococcal disease by age group in Scotland, 2000



- Peak incidence in the young and the elderly
- Peak case-fatality in < 1 years and ≥ 50 years

Graph 2.

Case-fatality rate by antibiotic susceptibility



(Minimal inhibitory concentrations (MIC) break points);-

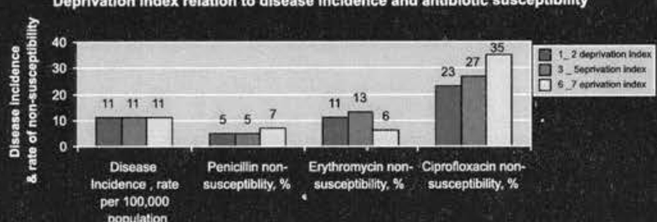
	Susceptible	Intermediate	Resistant
Penicillin:	0.06 μg/ml	0.1-1 μg/ml	≥2 μg/ml
Erythromycin:	≤0.5 μg/ml	1-2 μg/ml	≥4 μg/ml
Ciprofloxacin:	≤1 μg/ml -	≥1.1 μg/ml	

Intermediate and resistance isolates were defined as non-susceptible.

- Higher mortality in resistant infections
- No deaths in erythromycin resistant cases

Graph 3.

Deprivation index relation to disease incidence and antibiotic susceptibility

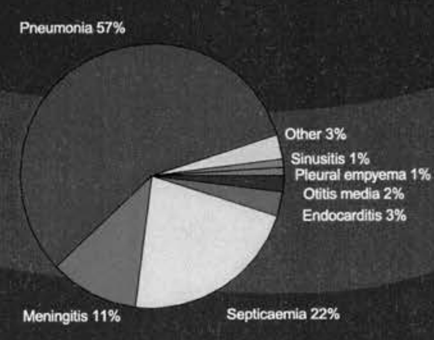


The Carstairs Deprivation Index is categorised into scores 1 to 7, with 1 being the most affluent and 7 being the most socio-economically deprived.

- No deprivation related difference
- Higher rates of ciprofloxacin resistance in less affluent groups

Graph 4.

Clinical presentations (leading diagnosis) of invasive pneumococcal disease



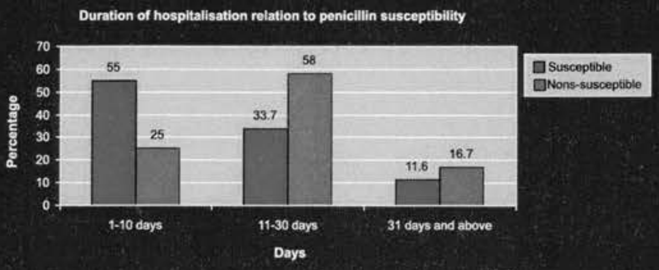
Scottish Centre for Infection and Environmental Health
Clifton House, Clifton Place, Glasgow G3 7LN
Tel: 0141 300 1100 Fax: 0141 300 1170

NHS SCOTLAND

Invasive pneumococcal disease in Scotland in 2000: use of record linkage to explore associations between patients and disease in relation to future vaccination policy

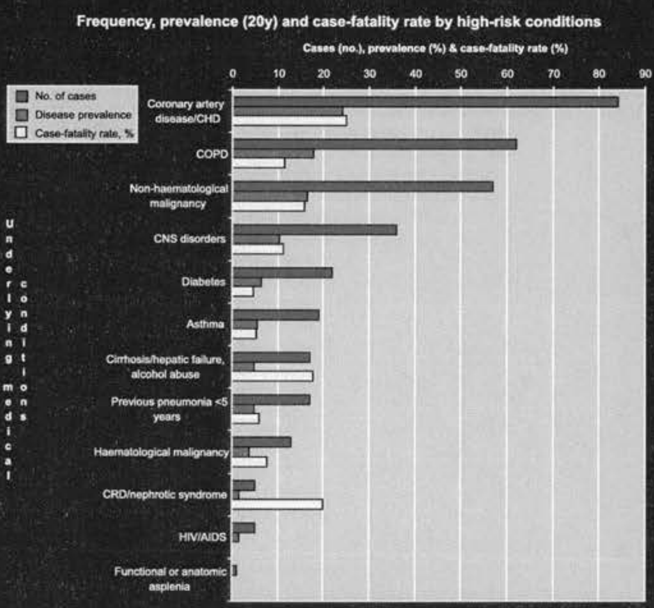
Moe H Kyaw[1,2], Peter Christie[1], Stuart Clarke[3], Jim Chalmers[4], Ian G Jones[1], Harry Campbell[2]

Graph 5.



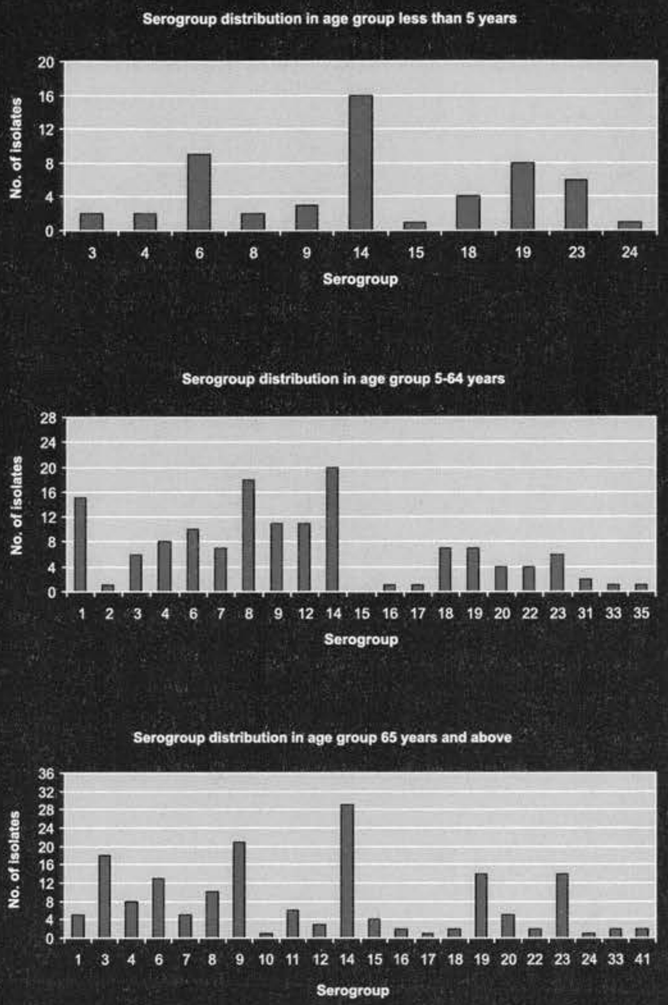
• Antibiotic resistance is associated with longer hospital stay

Graph 6.



• Higher case-fatality in coronary artery disease/CHD, hepatic/alcohol abuse and renal disease

Graph 7.



• Predominant serogroups:

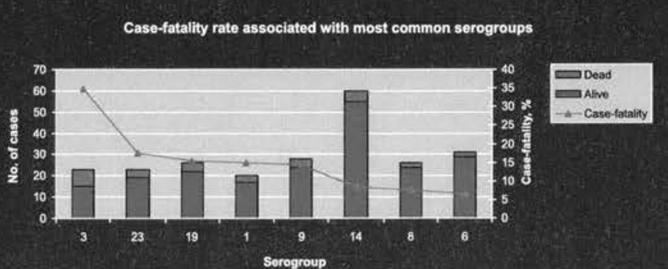
Serogroup 14 in all age groups

Serogroup 6, 18, 19, 23, in < 5 years

Serogroup 1, 8, 9, 12 in 5-64 years

Serogroup 9, 3, 19, 23 in ≥ 65 years

Graph 8.



• Serogroup 3 has higher case-fatality rate
• Serogroup 14 has lower case-fatality rate but is more common

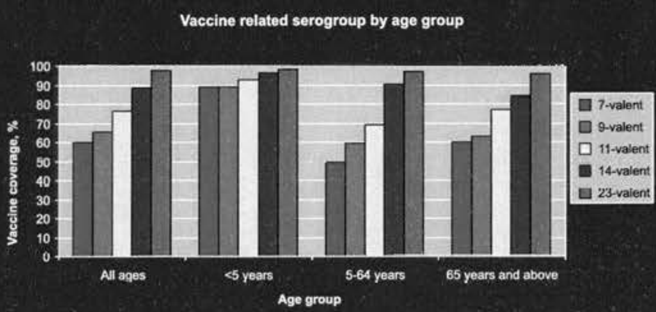
Scottish Centre for Infection and Environmental Health
Clifton House, Clifton Place, Glasgow G3 7LN
Tel: 0141 300 1100 Fax: 0141 300 1170

NHS SCOTLAND

Invasive pneumococcal disease in Scotland in 2000: use of record linkage to explore associations between patients and disease in relation to future vaccination policy

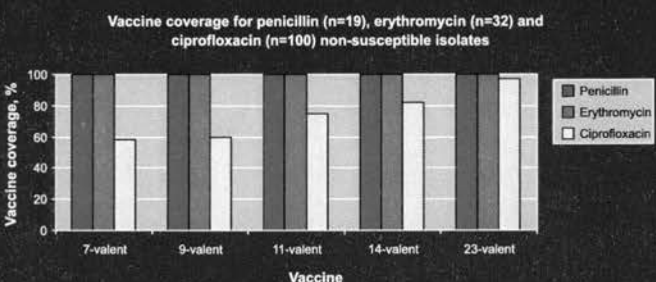
Moe H Kyaw[1,2], Peter Christie[1], Stuart Clarke[3], Jim Chalmers[4], Ian G Jones[1], Harry Campbell[2]

Graph 9.



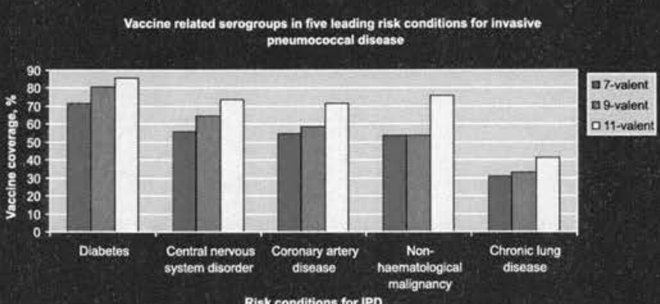
- Incomplete vaccine serotype coverage for > 5 years by 7-11 valent conjugate vaccines

Graph 10.



- Ciprofloxacin resistant strains better covered by 23-valent polysaccharide

Graph 11.



- Poorer coverage by conjugate vaccines in second highest risk group (chronic lung disease) although inadequate microbiological diagnosis may distort serotype coverage

Conclusions

- The risk of IPD is highest in young children, the elderly and persons with certain underlying medical conditions
- Conjugate vaccines cover the majority of serogroups causing IPD and antibiotic resistance in young children but coverage is lower in older age groups
- The routine use of conjugate and polysaccharide pneumococcal vaccines would prevent the majority of IPD, including those associated with antibiotic resistant strains
- This methodology provides a unique opportunity to investigate associations between patients and the epidemiological features of pneumococci
- It can be used as ongoing active long-term surveillance programme for monitoring the impact of vaccination on pneumococci

Acknowledgements

The Wyeth Vaccines (UK) and the Chief Scientist Office in Scotland funded this research.

Correspondence to Moe H Kyaw

Moe.Kyaw@scieh.csa.scot.nhs.uk

Tel: 0141 300 1184

[1] Scottish Centre for Infection and Environmental Health (SCIEH), Glasgow, UK
[2] University of Edinburgh, Public Health Sciences, Edinburgh, UK
[3] Scottish Meningococcus and Pneumococcus Reference Laboratory (SMPRL), UK
[4] Information and Statistics Division of the Common Services Agency, Edinburgh, UK

h. Glossary

Definitions

Serotype: The pneumococcus has 90 serotypes and 45 serogroups (section:1.1.1). Although serogroups and types are differed, the term “serotype” was used consistently in the study.

Antibiotic non-susceptibility: The cut off point for antibiotic susceptibity is divided into three levels, sensitive, intermediate resistant and high-level resistant. The term “antibiotic non-susceptibity” refers to the latter two categories for this study.

Invasive disease: This includes cases where the pneumococcus is isolated from normally sterile body sites such as cerebrospinal fluid, blood or joint fluid.

Invasive non-meningitic bacterial disease: This includes cases where the pneumococcus, meningococcus, Group B streptococcus, *Haemophilus influenzae* or *Listeria monocytogenes* are isolated from blood or other normally sterile sites but not from cerebrospinal fluid.

i. List of studies performed by author at SCIEH

1. Serotypes/groups distribution and antimicrobial resistance of invasive pneumococcal isolates: implications for vaccine strategies

2. Pneumococcal polysaccharide vaccination: opinion of general practitioners and hospital doctors in Scotland, 1999-2000

3. Non-invasive pneumococcal disease and antimicrobial resistance: vaccine implications

4. Incidence of invasive pneumococcal disease in Scotland, 1988-99

5. The changing epidemiology of bacterial meningitis and invasive non-meningitic bacterial disease in Scotland, 1983-99

6. Prevalence of moderate penicillin resistant invasive *Neisseria meningitidis* infection in Scotland, 1994-99

7. Invasive meningococcal disease in Scotland, 1994 to 1999: emphasis on group B meningococcal disease

8. Influenza and pneumococcal vaccine distribution and use in primary care and hospital settings in Scotland: coverage, practice and policies

9. A survey of vaccine coverage and antibiotic prophylaxis in splenectomised patients in Scotland

10. Influenza and pneumococcal vaccination coverage and policies in nursing home in Scotland

11. Prevalence of penicillin non-susceptible invasive pneumococcal disease in the elderly in Scotland, 1992-1999

12. Evaluation of serious infection and survival time after splenectomy in Scotland, 1988-98

13. Epidemiology of invasive pneumococcal disease in young children in Scotland, 1999-2001: implications for vaccination policies and strategies

14. Invasive pneumococcal disease in adults in Scotland, 1999-2001: use of record linkage to explore associations between patients and disease in relation to future vaccination policy

j. Copy of published articles by author related to this thesis

Epidemiol. Infect. (2000), **125**, 561–572. Printed in the United Kingdom

Serotypes/groups distribution and antimicrobial resistance of invasive pneumococcal isolates: implications for vaccine strategies

M. H. KYAW[1,3]*, S. CLARKE[2], G. F. S. EDWARDS[2], I. G. JONES[3] AND H. CAMPBELL[1]

[1] *University of Edinburgh, Public Health Sciences, Edinburgh*
[2] *Scottish Meningococcus and Pneumococcus Reference Laboratory, Glasgow*
[3] *Scottish Centre for Infection and Environmental Health, Glasgow*

(*Accepted 24 July 2000*)

SUMMARY

Based on the invasive pneumococcal isolates referred to reference laboratories in Scotland in 1988–99, we identified the distribution of serotypes/groups and their antimicrobial resistance patterns in order to evaluate the coverage of polysaccharide and the new pneumococcal conjugate vaccines. A total of 5659 invasive isolates were included. Of these, 5124 (90·5%) were blood isolates, 308 (5·5%) were CSF isolates, 143 (2·5%) were blood and CSF and 84 (1·5%) were other normally sterile isolates. The most prevalent 11 serotypes/groups were 14, 9, 19, 6, 23, 1, 3, 4, 7, 8 and 18, in numerical order. These accounted for 84% of total serotypes/groups.

The serotypes/groups included in the 23 and 14-valent polysaccharide vaccines accounted for 96% and 88% of all isolates. Both vaccines accounted for 98% of penicillin non-susceptible and 100% of erythromycin non-susceptible isolates. The 7, 9, and 11-valent conjugate vaccines covered 61, 68 and 80% of invasive isolates respectively. The coverage of these vaccines was substantially higher in youngest age group with 84, 86 and 93% of invasive isolates in children < 2 years included in the 7, 9 and 11-valent conjugate vaccines compared with 58, 64 and 77% in adults ⩾ 65 years of age.

The serotype/group distribution of invasive isolates in Scotland varied from year to year over the period 1993–9. The coverage of the 23-valent vaccine remained above 95% in each year but the coverage of the 7, 9 and 11-valent conjugate vaccines showed more marked fluctuation with coverage as low as 53, 60 and 75% in some years. Continued surveillance of invasive pneumococcal isolates is required to inform the development of appropriate vaccine strategies to prevent pneumococcal disease in Scotland.

INTRODUCTION

Despite the availability of effective antibiotics, invasive pneumococcal disease remains a serious public health problem worldwide. *Streptococcus pneumoniae* is a leading cause of bacteraemia and meningitis [1, 2] particularly among the very young and elderly and those with chronic medical conditions [3]. The current 23-valent polysaccharide pneumococcal vaccine covers at least 90 and 88% of serotypes/groups causing invasive pneumococcal disease in the UK [4] and US [5, 6] respectively. However, this vaccine is poorly immunogenic in children < 2 years old, the age group with the highest burden of invasive pneumococcal disease [7]. Therefore, new 7 to 11-valent conjugate pneumococcal vaccines are now

* Author for correspondence: Clifton House, Clifton Place, Glasgow, G3 7LN.

being developed and evaluated [8]. In addition, conjugate pneumococcal vaccines may have a future role in protecting the elderly and adults with conditions placing them at increased risk of pneumococcal disease.

The effectiveness of polysaccharide and conjugate vaccines is dependent on the distribution of vaccine serotypes in the population being immunized [9]. Therefore, knowledge of the distribution of pneumococcal serotypes/groups within a defined population is important in developing rational vaccine policy for the future use of conjugate pneumococcal vaccines in the prevention of invasive pneumococcal disease. This paper reviews population based data on *Streptococcus pneumoniae* isolates identified from sterile body site specimens in Scotland during the period 1988–99 and examines the seroepidemiological characteristics of invasive pneumococcal disease.

METHODS AND MATERIALS

Background

The data for this study were obtained from Scottish Centre for Infection and Environmental Health (SCIEH) and Scottish Meningococcus and Pneumococcus Reference Laboratory (SMPRL). SCIEH serves as a national surveillance centre for monitoring infectious diseases and environmental hazards. Reports from laboratories throughout Scotland are received by SCIEH on a weekly basis. SMPRL is the national reference laboratory for pneumococcal disease. It has been established to enhance national surveillance for these diseases and has excellent links with microbiology laboratories throughout Scotland. It acts as a national centre for serotyping and antibiotic sensitivity testing of pneumococcal isolates. Laboratory records of *Streptococcus pneumoniae* reported to SCIEH (1988–1998/9) and the pneumococcal isolates received routinely by SMPRL (1993–1998/9) from all diagnostic laboratories in Scotland have been combined in a single database.

Study data

Only invasive isolates (blood, cerebrospinal fluid (CSF) and other normally sterile sites) were included in this study. Duplicate records in SCIEH and SMPRL datasets were excluded. The Danish system of nomenclature was used for reporting pneumococcal serotypes/groups in both data bases. Isolates that had values of minimal inhibitory concentration (MIC) $\leqslant 0{\cdot}06\ \mu g/ml$, between $0{\cdot}12$ and $1{\cdot}0\ \mu g/ml$ and $2{\cdot}0\ \mu g/ml$ or higher were defined as sensitive, intermediate, and high level penicillin resistance respectively. Isolates with MICs of intermediate and resistant levels were described as non-susceptible. Pneumococcal isolates that had erythromycin level of $< 1\ \mu g/ml$ and $> 1\ \mu g/ml$ were recorded as sensitive and resistant respectively. The MICs were determined on the receipt of organism with the use of standard agar dilution MIC method in 1992–3 and the E-test method (Cambridge Diagnostics, Cambridge UK) since 1994.

Statistical analysis

Data analysis of pneumococcal isolates, serotypes/groups, specimen type, vaccine serotypes/groups and antimicrobial resistance were performed on the combined study dataset using SPSS version 8. 95% confidence intervals were calculated for the coverage of vaccines in different age groups during 1993–9.

RESULTS

A total of 17628 *Streptococcus pneumoniae* cases were recorded in the SCIEH and SMPRL databases over the study period. After removal of duplicate records, 10150 cases remained. Of these, only 5659 cases were from blood, CSF and other sterile site specimens and were included in the study. Of the 5659 invasive isolates, 5124 (90·5%) were blood isolates, 308 (5·5%) were CSF isolates, 143 (2·5%) were isolated from both blood and CSF, and 84 (1·5%) were other sterile site isolates (Table 1). A high proportion, 2499 (44·2%) were from elderly $\geqslant 65$ years old and only 661 (11·7%) were from children $\leqslant 5$ years old. 2601 (46%) were from females, 2886 (51%) from males and 172 (3%) sex unknown were included. The median and mean age of patients was 63 and 54 years old respectively. Information on serotypes/groups was available for 1531 isolates. Of these, only 105 (6·9%) isolates had their serotype/group reported during 1988–92. However, a high proportion, 1426 (93·1%) isolates had their serotype/group recorded in 1993–99 due to the establishment of SMPRL in 1992/3. The distribution among the 15 Health Boards in Scotland of isolates whose serotypes/groups were determined was as follows: Greater Glasgow, 428; Lothian, 400; Lanarkshire, 235; Grampian, 120; Ayrshire and Arran, 88; Argyll and Clyde, 60; Forth

Table 1. *Number of pneumococcal isolates from sterile sites*

	No. of isolates (%)				
Year	Total	Blood	CSF*	Blood +CSF	Others†
1988	296	248	23	23	2
1989	350	305	25	20	0
1990	343	300	28	14	1
1991	390	358	17	15	0
1992	441	403	27	10	1
1993	536	482	27	19	8
1994	622	560	38	14	10
1995	599	551	27	13	8
1996	617	563	34	7	13
1997	615	586	19	2	8
1998	646	590	32	5	19
1999‡	204	178	11	1	14
Total	5659 (100)	5124 (90·5)	308 (5·5)	143 (2·5)	84 (1·5)

* CSF, cerebrospinal fluid.

† Bone marrow, pleural aspirate, lung aspirate, pericardial fluid, bronchial aspirate.

‡ Data only available up to Aug. 1999.

Valley, 53; Tayside, 51; Highland, 44; Borders, 20; Fife, 13; Dumfries and Galloway, 12; Western Isles, 4; Orkney and Shetland, 0; and unknown area, 3.

Serotypes/groups distribution 1988/9

Most prevalent 11 serotypes/groups

The leading 11 serotypes/groups were identified among different age groups (Table 2). In all age groups, these serotypes/groups accounted for over 80% of all invasive pneumococcal isolates.

Overall, type 14 was the most prevalent serotype, accounting for about 10–32% of invasive isolates. Serotype 1 was the most prevalent in the age group 5–64 years accounting for 13% of invasive pneumococcal isolates.

Annual pattern of most prevalent serotypes/groups

The prevalence of individual serotypes/groups fluctuated from year to year of the period 1993–9 (Table 3). This shows an increase in serotype 14 and a decline in serotype 3 in recent years.

Prevalence of vaccine-related serotypes/groups

Coverage by 23-valent and 14-valent polysaccharide vaccines

The current 23-valent and previous 14-valent vaccines covered 96 and 88% of reported pneumococcal serotypes/groups isolated in all age groups in the study period. The reported coverage in individual age groups is shown in Table 4.

Coverage by 7, 9 and 11-valent conjugate pneumococcal vaccines

The 7-valent conjugate vaccine includes serotypes 4, 6B, 9V, 14, 18C, 19F and 23F [8]. Serotypes 1 and 5 are added in the 9-valent vaccine and 1, 3, 5, 7F in the 11-valent vaccine [10]. These 7, 9 and 11-valent conjugate vaccines covered 61, 68 and 80% of reported pneumococcal serotypes/groups isolated in all groups respectively. Coverage was substantially higher in the < 2 years than in older age groups (Table 4).

Coverage of invasive serotypes/groups with 23-valent polysaccharide and the 7-, 9- and 11-valent conjugate vaccines: annual fluctuation over the period 1993–9

The 23-valent polysaccharide vaccine covered > 90% of invasive isolates in all ages. However, the annual coverage of the 7, 9 and 11-valent conjugate vaccine showed substantial annual variation. Coverage was 59–97, 64–97 and 77–100% for 7, 9 and 11-valent conjugate vaccine in < 2 years age group, 42–69, 47–75 and 57–88% for 7, 9 and 11-valent conjugate vaccine in ⩾ 65 years age group and 53–73, 60–76 and 75–82% for 7, 9 and 11-valent conjugate vaccine for all ages (Table 5).

Table 2. *Most prevalent (11) pneumococcal serotypes/groups in different age groups*

Serotypes/ groups	No. of isolates (%)	Serotypes/ groups	No. of isolates (%)
< 2 years		⩾ 65 years	
14	69 (31·8)	14	83 (14·5)
6	38 (17·5)	19	61 (10·6)
19	22 (10·1)	3	56 (9·8)
23	22 (10·1)	9	53 (9·2)
9	14 (6·5)	23	47 (8·2)
18	10 (4·6)	4	41 (7·2)
7	8 (3·7)	6	41 (7·2)
4	7 (3·2)	1	35 (6·1)
3	6 (2·8)	8	26 (4·5)
1	5 (2·3)	22	19 (3·3)
8	2 (0·9)	7	18 (3·1)
Total*	203 (93·5)	Total*	480 (83·8)
Total†	217 (100)	Total†	573 (100)
⩽ 5 years		All ages	
14	72 (29·3)	14	254 (16·6)
6	40 (16·3)	9	144 (9·4)
23	24 (9·8)	19	140 (9·4)
19	23 (9·3)	6	133 (8·7)
18	18 (7·3)	23	126 (8·2)
9	16 (6·5)	1	114 (7·4)
7	10 (4·1)	3	104 (6·8)
1	9 (3·7)	4	94 (6·1)
4	8 (3·3)	7	70 (4·6)
3	6 (2·4)	8	64 (4·2)
8	2 (0·8)	18	40 (2·6)
Total*	228 (92·7)	Total*	1283 (83·8)
Total†	246 (100)	Total†	1531 (100)
5–64 years			
1	66 (13·2)		
9	55 (11·0)		
14	52 (10·4)		
7	36 (7·2)		
4	36 (7·2)		
23	31 (6·2)		
3	30 (6·0)		
8	29 (5·8)		
6	29 (5·8)		
19	28 (5·6)		
22	18 (3·6)		
Total*	410 (82)		
Total†	500 (100)		

* Total for top 11 serotypes/groups.
† Overall total.

Most prevalent serotypes/groups not included in the new 11-valent conjugate vaccine

Serotypes/group 8, 11, 12 and 22 were the most common nor-vaccine serotypes/groups, accounting for 178 (12%) of invasive isolates in all ages (Table 6). A higher proportion of them was recorded in those ⩾ 5 years of age.

Penicillin/erythromycin susceptibility

The distribution of serotypes/groups that were penicillin and erythromycin susceptible and non-susceptible is shown in Table 7. The prevalence of high level penicillin resistance is very low. Only two blood isolates were shown to have penicillin resistance. Both were serotype 14.

Table 3. *Most prevalent (11) serotypes/groups: annual variation (1993–9)*

Serotypes/ groups	No. of isolates 1993	1994	1995	1996	1997	1998	1999	Total
1	15	22	16	23	11	11	7	105
3	11	16	15	14	20	9	6	91
4	13	9	20	12	10	10	11	85
6	22	17	17	24	13	18	17	128
7	8	12	14	4	13	9	3	63
8	10	12	6	6	11	7	8	60
9	19	11	19	21	12	30	24	136
14	21	31	26	35	29	52	50	244
18	4	10	5	3	3	8	1	34
19	21	20	18	15	15	23	20	132
23	14	23	13	17	14	13	26	120
Others	30	46	32	32	30	27	31	228
Total*	158	183	169	174	151	190	173	1198
Total†	188	229	201	206	181	217	204	1426

* A total of top 11 serotypes/groups in each year.
† All total serotypes/groups in each year.

Table 4. *Vaccine coverage of pneumococcal serotypes/groups in different age groups*

Vaccines	No. of vaccine related isolates (%) < 2 years	⩽ 5 years	5–64 years	⩾65 years	All ages
23-valent	NA†	244 (99·2)	475 (95)	550 (96)	1476 (96·4)
14-valent	NA	232 (94·3)	427 (85·4)	481 (83·9)	1354 (88·4)
11-valent*	201 (92·6)	226 (91·9)	379 (75·8)	440 (76·8)	1221 (79·8)
9-valent*	187 (86·2)	210 (85·4)	313 (62·6)	366 (63·9)	1047 (68·4)
7-valent*	182 (83·9)	201 (81·7)	247 (49·4)	331 (57·8)	931 (60·8)
Total	217 (100)	246 (100)	500 (100)	573 (100)	1531 (100)

* Pneumococcal conjugate vaccine.
† NA, not applicable.

Erythromycin resistant serotypes included types 4, 6, 9, 14, 19 and 23. Of these, serotype 14 accounted for 81/108 (75%) of isolates. The most prevalent serotypes associated with penicillin intermediate resistance were types 6, 9, 14, 19 and 23, accounting for 97/105 (92%) of isolates.

Vaccine coverage of antibiotic susceptible and non-susceptible invasive pneumococcal isolates

The 23- and 14-valent polysaccharide vaccine provided 97–100% and 86–98% coverage of all penicillin susceptible and non-susceptible isolates respectively. The conjugate pneumococcal vaccines covered 58–79% and 94–100% of susceptible and non-susceptible isolates (Table 8). A similar pattern was noted for erythromycin sensitive and resistant isolates (Table 8).

DISCUSSION

There are very few contemporary data on the distribution of invasive pneumococcal serotypes/groups in the UK. This study reports seroepidemiological characteristics of invasive pneumococcal isolates referred to reference laboratories in Scotland over the period 1988–99. The 7, 9 and 11-valent conjugate vaccines are now undergoing clinical trials in both developed and developing countries [8].

Earlier data on safety and immunogenicity of conjugate vaccines are encouraging among infants, and young children, [11–16] adults, [17, 18] and those

Table 5. *Yearly coverage of pneumococcal vaccines for < 2 years old, ⩽ 5 years old, ⩾ 65 years old and all ages 1993–9*

	< 2 years				⩽ 5 years				⩾ 65 years				All ages			
	No. of vaccine related serotypes/groups (%)				No. of vaccine related serotypes/groups (%)				No. of vaccine related serotypes/groups (%)				No. of vaccine related serotypes/groups (%)			
Year	23	11*	9*	7*	23	11*	9*	7*	23	11*	9*	7*	23	11*	9*	7*
1993	26 (100)	24 (92·3)	23 (88·5)	22 (84·6)	27 (100)	25 (92·6)	25 (92·6)	24 (88·9)	47 (90·4)	42 (80·8)	39 (75)	35 (67·3)	180 (95·7)	148 (78·7)	129 (68·6)	114 (60·0)
95% CI	(87, 100)	(75, 99)	(70, 98)	(65, 96)	(87, 100)	(76, 99)	(76, 99)	(71, 98)	(79, 97)	(67, 90)	(61, 86)	(53, 80)	(92, 98)	(72, 84)	(61, 75)	(53, 68)
1994	35 (97·2)	34 (94·4)	32 (88·9)	29 (80·6)	42 (97·7)	41 (95·4)	38 (88·4)	33 (76·7)	73 (94·8)	44 (57·1)	36 (46·8)	32 (41·6)	220 (96·1)	171 (74·7)	143 (62·4)	121 (52·8)
95% CI	(85, 100)	(81, 89)	(74, 97)	(64, 92)	(88, 100)	(84, 99)	(75, 96)	(61, 88)	(87, 99)	(45, 68)	(35, 58)	(30, 53)	(93, 96)	(69, 80)	(56, 69)	(46, 60)
1995	22 (100)	17 (77·3)	14 (63·6)	13 (59·1)	26 (100)	21 (80·8)	18 (69·2)	17 (65·4)	77 (96·3)	70 (87·5)	55 (68·7)	48 (60)	193 (96·0)	163 (81·1)	134 (66·7)	118 (58·7)
95% CI	(85, 100)	(55, 92)	(41, 83)	(36, 79)	(87, 100)	(61, 93)	(48, 86)	(44, 83)	(89, 99)	(78, 94)	(57, 79)	(48, 71)	(92, 98)	(75, 86)	(60, 73)	(52, 66)
1996	29 (100)	29 (100)	28 (96·6)	28 (96·6)	33 (100)	31 (93·9)	30 (90·9)	30 (90·9)	80 (95·2)	68 (80·9)	58 (69)	48 (57·1)	199 (96·6)	168 (81·6)	150 (72·8)	127 (61·6)
95% CI	(88, 100)	(88, 100)	(82, 100)	(82, 100)	(89, 100)	(80, 99)	(76, 98)	(76, 98)	(88, 99)	(71, 89)	(58, 79)	(46, 68)	(93, 99)	(76, 87)	(66, 79)	(55, 68)
1997	23 (100)	22 (95·7)	22 (95·7)	22 (95·7)	29 (100)	27 (93·1)	27 (93·1)	25 (86·2)	84 (98·8)	66 (77·7)	46 (54·1)	44 (51·8)	175 (96·7)	142 (78·5)	109 (60·2)	96 (53·0)
95% CI	(85, 100)	(78, 100)	(78, 100)	(78, 100)	(88, 100)	(77, 99)	(77, 99)	(68, 96)	(94, 100)	(67, 86)	(43, 65)	(41, 63)	(93, 99)	(72, 84)	(53, 67)	(45, 60)
1998	38 (97·4)	36 (92·3)	35 (89·7)	35 (89·7)	41 (97·6)	39 (92·9)	38 (90·5)	38 (90·5)	74 (97·4)	62 (81·6)	55 (72·4)	51 (67·1)	209 (96·3)	179 (82·5)	165 (76·0)	154 (70·9)
95% CI	(87, 100)	(79, 98)	(76, 97)	(76, 97)	(87, 100)	(81, 99)	(77, 97)	(77, 97)	(91, 100)	(71, 90)	(61, 82)	(55, 77)	(93, 98)	(77, 87)	(70, 82)	(65, 77)
1999	29 (100)	26 (89·7)	23 (79·3)	23 (79·3)	31 (100)	27 (87·1)	23 (74·2)	23 (74·2)	73 (97·3)	56 (74·7)	53 (70·7)	52 (69·3)	201 (98·5)	165 (80·9)	156 (76·5)	149 (73·0)
95% CI	(88, 100)	(73, 98)	(60, 92)	(60, 92)	(89, 100)	(70, 96)	(55, 68)	(55, 88)	(91, 100)	(63, 84)	(59, 81)	(58, 79)	(96, 100)	(75, 86)	(70, 82)	(65, 79)

* Pneumococcal conjugate vaccines; CI, confidence interval.

with medical conditions which compromise immune function [19–24]. The result of the first large-scale clinical trial from Southern California showed that the 7-valent conjugate vaccines had 100% efficacy in prevention of invasive pneumococcal infections in infants and children caused by the vaccine serotypes/groups [25]. This suggests that the 7-valent conjugate vaccine may soon be licensed for use in infants and children in developed countries. It has been proposed that pneumococcal conjugate vaccines may also have an important role in preventing pneumococcal disease in the elderly [26].

Therefore, an understanding of the serotype distribution of pneumococcal isolates will be crucial in developing appropriate immunization policy for different age groups in Scotland. This study reports on the coverage of serotypes/groups in the current polysaccharide and the new conjugate pneumococcal vaccines in Scotland.

Serotypes/groups distributions

We found that the most prevalent serotypes (14, 9, 19, 6, 23, 1, 3, 4, 7, 8 and 18) accounted for over 82–94% of total serotypes/groups in all age groups. Inclusion of these serotypes/groups in the new 11-valent conjugate vaccine will therefore cover > 80% of invasive pneumococcal serotypes/groups in children, adults and the elderly. This is similar to previous findings from the US [27, 28], Europe [29–31], New Zealand [32] and Australia [33]. In contrast, data from Africa and Asia showed that serotypes 1 and 5 were the predominant invasive isolates [9, 34].

The major serotypes/groups in different age groups included serotypes/groups 14, 6, 19, 23 and 9 in < 2 years, 14, 6, 23, 19 and 18 in ⩽ 5 years, 1, 9, 14, 7 and 4 in 5–64 years old and 14, 19, 3, 9 and 23 in ⩾ 65 years old. In common with some other studies, our data indicate that type 14 was the most common infectious serotype in all age groups [9, 35].

Among the age group 5–64 years, serotype 1 was the main cause of invasive disease, accounting for about 13% of cases. Earlier reports from US have observed that serogroup 12 is the most frequent cause of bacteraemia in patients with pneumonia [36] and associated with outbreaks in both children [37] and adults [38]. In addition, surveillance data from the US and Europe indicate that a shift of serotypes distribution can occur over time [39]. Types 1–3 were the most prevalent isolates in bacteraemic cases at the beginning of the century, accounting for c. 70% of

Table 6. *Common prevalent serotypes/groups in Scotland not included in the new 11-valent conjugate vaccine*

Serotypes/ groups	< 2 years	⩽ 5 years	5–64 years	⩾ 65 years	All ages
8	2	2	29	26	64
11	0	1	13	14	33
12	3	3	18	12	35
22	3	6	18	19	46
Total*	8 (3·7)	12 (4·9)	78 (15·6)	71 (12·4)	178 (11·6)
Total†	217 (100)	246 (100)	500 (100)	573 (100)	1531 (100)

* Total, percentages given in parentheses for nonvaccine serotypes in the 11-valent vaccine.
† Overall total, percentages given in parentheses.

invasive isolates [40, 41]. However, since 1979, these isolates have been very much less common (< 5%) [42], and serotypes 6, 14, 18 and 23 are more frequently isolated in the US [43] and Europe [30, 31, 44].

This suggests that continued surveillance systems are essential to monitor the stability of pneumococcal serotypes/groups distribution in Scotland. Review of serotype data from sterile site specimens from 16 countries showed that serotypes/groups 14, 6 and 19 were consistently found in all geographic locations [9]. However, the important invasive serotypes in children < 5 years of age varied, with serotype 18 most prevalent in developed countries, type 23 in Europe and serotypes 1 and 5 in developing countries. These differences in serotypes/groups distribution impose a challenge for designing a conjugate vaccine with appropriate serotypes distribution for all locations.

The 23- and 14-valent pneumococcal polysaccharide vaccines

The increase in antibiotic resistant pneumococcal [45] and the high burden of invasive pneumococcal disease among high-risk groups has been documented consistently [10]. Pneumococcal polysaccharide vaccines have been estimated by case-control and indirect cohort studies, to be 50–80% effective in reducing invasive pneumococcal disease in the elderly and in adults with chronic medical conditions [46]. We have found that the 23-valent and (previous) 14-valent polysaccharide vaccines covered 97% and > 83% respectively of invasive isolates. This is similar to published data from other parts of UK, Europe and North America; 91–97% in England and Wales, and Scotland [35, 47, 48], 89–97% in Sweden [49], > 85% in the US [5, 27], > 90% in Canada [50], 95% in Finland [31] and 92% in Denmark [30] for older children and adults.

Limited data are available on serotypes/groups distribution in Asia and Africa where mortality rates from pneumococcal disease are high. The available data from Asian countries show a large variation in the proportion of invasive pneumococcal isolates covered by the 23-valent vaccine: 75% in Bangladesh, 70·5% in Korea [51] and 62·9% in Taiwan [52].

Conjugate vaccines

Conjugate pneumococcal vaccines are undergoing phase I, II, and III clinical trials in the US, South Africa, Israel, Gambia, Finland and Philippines [8, 53]. Based on serological data, pneumococcal conjugate vaccines appear to produce a more immunogenic response in infants, the elderly, and immunocompromised individuals than pneumococcal polysaccharide vaccines [26]. In addition, findings from South Africa [54] Gambia [55] and Israel [56] reveal that conjugate vaccines reduce nasopharyngeal carriage of vaccine serotypes. Therefore, it may be possible to achieve herd immunity by widespread use of conjugate vaccines in the future. Data from the US suggest that the serotypes included in the current 7-valent conjugate vaccine could prevent 86% and 83% of pneumococcal bacteraemia and meningitis in children < 6 years old [43]. A previous survey in England and Wales [4, 48] noted that about 73% of isolates found in children ⩽ 2 years old were included in the 9-valent conjugate vaccines. We found a higher coverage of > 90% with the 11-valent conjugate vaccine and > 80% with the 7–9 valent conjugate vaccines for children < 2 years of age. The 11-valent vaccine also covers serogroups

Table 7. *Penicillin and erythromycin susceptible and non-susceptible invasive pneumococcal serotypes/groups*

Penicillin susceptibility						Erythromycin susceptibility					
		No. of isolates from sterile sites						No. of isolates from sterile sites			
MIC	Serotypes/ groups	CSF	Blood	Others	Total	MIC	Serotypes/ groups	CSF	Blood	Others	Total
	1	3	90	4	97		1	2	74	5	81
	2	—	6	—	6		2	—	6	—	6
	3	7	67	6	80		3	8	56	5	69
	4	7	69	3	79		4	6	53	3	62
	5	—	1	—	1		5	—	2	—	2
	6	17	66	3	86		6	13	63	4	80
	7	5	51	1	57		7	5	43	1	49
	8	8	45	1	54		8	7	38	1	46
S*	9	8	83	1	92	S	9	7	88	81	176
	10	—	9	1	10		10	—	8	—	8
	11	3	23	1	27		11	2	20	—	22
	12	5	24	—	29		12	4	21	—	25
	13	—	2	—	2		13	—	1	—	1
	14	25	151	9	185		14	5	83	8	96
	15	1	14	1	16		15	1	12	—	13
	16	1	5	—	6		16	1	4	—	5
	17	1	3	—	4		17	1	3	—	4
	18	10	23	—	33		18	7	18	—	25
	19	11	89	3	103		19	9	79	5	93
	20	—	15	—	15		20	—	14	—	14
	21	—	1	—	1		21	—	1	—	1
	22	5	28	—	33		22	5	22	—	27
	23	14	65	5	84		23	10	62	6	78
	24	2	3	—	5		24	1	3	—	4
	27	—	—	1	1		27	—	—	1	1
	29	—	4	—	4		29	—	4	—	4
	31	1	6	—	7		31	1	5	—	6
	38	1	9	—	10		38	1	6	—	7
	34	—	3	1	4		34	—	3	1	4
	35	—	3	—	3		35	—	2	—	2
	38	—	5	—	5		38	—	4	—	4
	41	—	1	—	1		41	—	1	—	1
	42	—	1	—	1		42	—	1	—	1
Total		135	965	41	1141			96	800	121	1017
	1	—	—	1	1		1	—	—	—	—
	3	1	1	1	3		3	—	—	—	—
	4	—	—	—	—		4	—	1	—	1
	5	—	1	—	1		5	—	—	—	—
	6	—	19	3	22		6	—	10	2	12
I*	8	—	1	—	1	R	8	—	—	—	—
	9	1	23	9	33		9	—	3	2	5
	14	—	18	2	20		14	16	63	2	81
	15	—	1	—	1		15	—	—	—	—
	19	—	8	2	10		19	1	4	—	5
	23	—	9	3	12		23	—	3	1	4
	29	—	1	—	1		29	—	—	—	—
Total		2	82	21	105			17	84	7	108
R*	14		2		2						
Total		—	2	—	2						

* S, sensitive isolates; I, intermediate isolates; R, resistant isolates.

Table 8. *Penicillin and erythromycin susceptible and non-susceptible pneumococcal serotypes/groups covered by the vaccines. No. (%) of vaccine-related isolates*

	Penicillin*				Erythromycin		
Vaccines	S	I	R	Total	S	R	Total
23	1100 (97·3)	104 (99·0)	2 (100)	1206 (96·6)	910 (96·3)	108 (100)	1018 (96·7)
14	985 (86·3)	103 (98·1)	2 (100)	1090 (87·3)	813 (86·0)	108 (100)	921 (87·5)
11†	897 (78·6)	102 (97·1)	2 (100)	1001 (80·2)	738 (78·1)	108 (100)	846 (80·3)
9†	760 (66·6)	99 (94·3)	2 (100)	861 (69)	620 (65·6)	108 (100)	728 (69·1)
7†	662 (58·0)	97 (97·4)	2 (100)	761 (61)	537 (56·8)	108 (100)	645 (61·3)

* S, sensitive isolates; I, intermediate isolates; R, resistant isolates (non-susceptible isolates = intermediate and resistant isolates).

† Pneumococcal conjugate vaccine.

3, 19 and 23 that were mainly responsible for otitis media in US, Canadian and European children [57].

Therefore, it is unlikely that pneumococcal conjugate vaccines for children need to include > 11 serotypes. However, a substantially lower coverage was observed, (about 50–57% with 7-valent, 62–63% with 9-valent and 75–76% with 11-valent conjugate vaccines) in those above 5 years (including elderly ⩾ 65 years). In addition coverage in this age group fluctuated from year to year, over the period 1993–9.

Serotypes/groups 8, 11, 12 and 22 were the most common invasive isolates not present in the 11-valent vaccine, accounting for 15·6 and 12·4% of isolates in 5–64 years old and ⩾ 65 years old respectively. Including these serotypes/groups in the 11-valent could increase the vaccine coverage to > 80% of invasive isolates in these age groups. However, a larger number of serotypes attached to a carrier protein could lead to poorer immunogenicity and possibly promote serious local reactions [58]. Further research is required on this issue. Furthermore, concerns about the replacement of vaccine serotypes by serotypes not in the vaccine have been expressed [55] and are now under investigation [54].

Drug susceptible pneumococcal isolates

Pneumococcal isolates that are resistant to penicillin and other antimicrobial drugs have been detected on all continents [59, 60]. Serogroups 6, 19 and 23 have been most associated with drug resistance [59, 61].

In the present study, serotypes/groups 6, 14, 19 and 23 were the most commonly associated with intermediate resistance and serotype 14 with penicillin and erythromycin resistant isolates. A previous survey from England and Wales identified similar serotypes/groups (23F, 6B, 19A, 19C, 19F and 23F) associated with intermediate or high penicillin resistance. Resistance to erythromycin was associated with serotypes/groups (3, 5, 9, 14, 19 and 22) in 1990 and with serotypes/groups (3, 6, 14, 15, 19 and 23) in 1995 [48]. Other UK studies also indicated that type 23, 9 and 6 were most commonly associated with penicillin resistance [62–64].

The commonest serotypes/groups associated with penicillin resistance in other countries included 9, 23 in Canada [50, 65], 6, 14, 19 and 23 in South Africa, Spain and Hungary [45] and 6B, 9V, 14, 19F and 23F in the US [66]. In general, these data suggest that the main serotypes patterns associated with lack of susceptibility to penicillin and erythromycin are similar in most geographical areas. However, recently, type 15 in Spain and type 10 [67] and 16 and 13 in Kenya [68, 69] have been found to be associated with penicillin resistance.

Our data show that the 23-valent vaccine covers ⩾ 99% of invasive isolates which were found to be non-susceptible to penicillin or resistant to erythromycin. The 11-valent conjugate vaccine covered > 78%, and 7- and 9-valent covered > 56% of non-susceptible and resistant invasive isolates for both drugs. Therefore, a greater use of 23-valent or the new 11-valent conjugate vaccine could possibly reduce the majority of penicillin non-susceptible and erythromycin resistant invasive pneumococcal isolates.

The data presented in this study should be helpful in predicting the potential impact of pneumococcal vaccines on invasive pneumococcal disease. There is a need for complementary data on isolates associated with important non-invasive pneumococcal disease such as otitis media in order to inform future policies on the prevention of pneumococcal disease in Scotland.

ACKNOWLEDGEMENTS

We gratefully acknowledge Dr Claire Bramley, John Mooney, Lynn Young and Mary Locking for their advice and assistance for statistical analysis.

REFERENCES

1. George G. Epidemiology of pneumococcal disease. In: Mayon-White RT, ed. The clinical impact of pneumococcal disease and strategies for its prevention. Royal Society of Medicine International Congress and Symposium series, **210**. London: Royal Society of Medicine, 1995: 1–5.
2. Schuchat A, Robinson K, Wenger J, et al. Bacterial meningitis in the United States in 1995. NEJM 1997; **337**: 970–6.
3. MMWR. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997; **46**: 1–24.
4. Johnson AP, Speller DCE, George RC, et al. Prevalence of antibiotic resistance and serotypes in pneumococci in England and Wales: results of observational surveys in 1990 and 1995. BMJ 1996; **312**: 1454–6.
5. Robbins J, Austrian R, Lee CJ, et al. Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. J Infect Dis 1983; **148**: 1136–59.
6. Breiman R, Butler J, Tenover FC, et al. Emergence of drug resistant pneumococcal infections in the United States. JAMA 1994; **271**: 1831–5.
7. Gray B, Dillion HJ. Clinical and epidemiologic studies of pneumococcal infection in children. Pediatr Infect Dis J 1986; **5**: 201–7.
8. Eskola J, Anttila M. Pneumococcal conjugate vaccines. Pediatr Infect Dis J 1999; **18**: 543–51.
9. Sniadack DH, Schwartz B, Lipman H, et al. Potential interventions for the prevention of childhood pneumonia: geographic and temporal differences in serotype and serogroup distribution of sterile site pneumococcal isolates from children – implications for vaccine strategies. Pediatr Infect Dis J 1995; **14**: 503–10.
10. Fedson D, Musher D, Eskola J. Pneumococcal vaccine. In: Plotkin SA, Orenstein WA, eds. Vaccines. Philadelphia: W.B. Saunder Company, 1999: 553–607.
11. Steinhoff M, Edwards K, Keyserling H, et al. A randomized comparison of three bivalent *Streptococcus pneumoniae* glycoprotein conjugate vaccines in young children: effect of polysaccharide size and linkage characteristics. Pediatr Infect Dis J 1994; **13**: 368–72.
12. Kayhty H, Ahman H, Ronnberg P-R, et al. Pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine is immunogenic in infants. J Infect Dis 1995; **172**: 1273–8.
13. O'Brien K, Steinhoff M, Edwards K, et al. Immunologic priming of young children by pneumococcal glycoprotein conjugate, but not polysaccharide, vaccines. Pediatr Infect Dis J 1996; **15**: 425–30.
14. Leach A, Ceesay SJ, Banya WAS, et al. Pilot trial of a pentavalent pneumococcal polysaccharide/protein conjugate vaccine in Gambian infants. Pediatr Infect Dis J 1996; **15**: 333–9.
15. Anderson E, Kennedy DJ, Geldmacher KM, et al. Immunogenicity of heptavalent pneumococcal conjugate vaccine in infants. J Pediatrics 1997; **128**: 649–53.
16. Ahman H, Kayhty H, Lehtonen H, et al. *Streptococcus pneumoniae* capsular polysaccharide-diphtheria toxoid conjugate vaccine is immunogenic in early infancy and able to induce immunologic memory. Pediatr Infect Dis J 1998; **17**: 211–6.
17. Fattom A, Lue C, Szu SC, et al. Serum antibody response in adult volunteers elicited by injection of *Streptococcus pneumoniae* type 12F polysaccharide alone or conjugated to diphtheria toxoid. Infect Immun 1990; **58**: 2309–12.
18. Schneerson R, Robbins JB, Parke JC, et al. Quantitative and qualitative analyses of serum antibodies elicited in adults by *Haemophilus influenzae* type b and pneumococcus type 6A capsular polysaccharide-tetanus toxoid conjugates. Infect Immun 1986; **52**: 519–28.
19. Chan C, Morline D, George S, et al. Pneumococcal conjugate vaccine primes for antibody responses to polysaccharide pneumococcal vaccine after treatment of Hodgkin's disease. J Infect Dis 1996; **173**: 256–8.
20. King JJ, Vink P, Farley JJ, et al. Comparison of the safety and immunogenecity of a pneumococcal conjugate vaccine with a licensed polysaccharide vaccine in human immunodeficiency virus and non-human immunodeficiency virus infected children. Pediatr Infect Dis J 1996; **15**: 192–6.
21. King JJ, Vink P, Farley JJ, et al. Safety and immunogenicity of three doses of a five-valent pneumococcal conjugate vaccine in children younger than two years with and without human immunodeficiency virus infection. Pediatrics 1997; **99**: 575–80.
22. King JC, Vink PE, Chang IH, et al. Antibody titers eight months after three doses of a five-valent pneumococcal conjugate vaccine in HIV and non-HIV-infected children less than two years of age. Vaccine 1998; **16**: 361–5.
23. Vernacchio L, Neufeld EJ, MacDonald K, et al. Combined schedule of 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal vaccine in children and young adults with sickle cell disease. J Pediatr 1998; **133**: 275–8.
24. Sarnaik S, Kaplan J, Schiffman G, et al. Studies on pneumococcus vaccine alone or mixed with DTP and a pneumococcus type 6B and *Haemophilus influenzae* type b capsular polysaccharide tetanus toxoid conjugates in two- to five-year-old children with sickle cell anaemia. Pediatr Infect Dis J 1990; **9**: 181–6.
25. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000; **19**: 187–95.

26. Klein DL, Ellis RW. Conjugate vaccines against *Streptococcus pneumoniae*. In: Levine MM, Woodrow GC, Kaper JB, Cobon GS, eds. New generation vaccines, 2nd edn. New York: Marcel Dekker Inc. 1997: 503–25.
27. Butler J, Breiman R, Campbell J, Lipman H, Broome C, Facklam R. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. JAMA 1993; **270**: 1826–31.
28. Zangwill K, Vadheim C, Vannier AM, et al. Epidemiology of invasive pneumococcal disease in Southern California: implications for the design and conduct of a pneumococcal conjugate vaccine efficacy trial. J Infect Dis 1996; **174**: 752–9.
29. Fenoll A, Bourgon C, Munoz R, Vicioso D, Casal J. Serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae* isolates causing systemic infections in Spain, 1979–1989. Rev Infect Dis 1991; **13**: 56–60.
30. Nielsen S, Henrichsen J. Incidence of invasive pneumococcal disease and distribution of capsular types of pneumococci in Denmark, 1989–1994. Epidemiol Infect 1996; **117**: 411–6.
31. Sankilampi U, Herva E, Haikala R, et al. Epidemiology of invasive *Streptococcus pneumoniae* infections in adults in Finland. Epidemiol Infect 1997; **118**: 7–15.
32. Mansoor O. Pneumococcal infections in New Zealand. Vaccine 1999; **17**: S122–3.
33. Hogg G, Strachan J. Pneumococcal infections in Victoria, Australia. Vaccine 1999; **17**: S119–21.
34. Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, Part I. Clin Infect Dis 2000; **30**: 100–21.
35. Smith M, Stuart J, Andrews NJ, et al. Invasive pneumococcal infection in South and West England. Epidemiol Infect 1998; **120**: 117–23.
36. Austrian R. Some observation on the pneumococcus and on the current status of pneumococcal disease and its prevention. Rev Infect Dis 1981; **3**: S1–17.
37. Cherian T, Stenhoff M, Harrison L, Rohn D, Dougal L, Dick J. A cluster of invasive pneumococcal disease in children in child care. JAMA 1994; **271**: 695–8.
38. MMWR. Outbreak of invasive pneumococcal disease in a jail – Texas 1989. MMWR 1989 ; **38**: 733–4.
39. Kalin M. Pneumococcal serotypes and their clinical relevance. Thorax 1998; **53**: 159–62.
40. Finland M, Barnes M. Changes in occurrence of capsular serotypes of *Streptococcus pneumoniae* at Boston City hospital during selected years between 1935 and 1974. J Clin Microbiol 1977; **5**: 154–66.
41. Watson D, Musher D, Verhoef J. Pneumococcal virulence factors and host immune responses to them. Eur J Clin Microbiol Infect Dis 1995; **14**: 479–90.
42. Barry M, Craven D, Finland M. Serotypes of *Streptococcus pneumoniae* isolated from blood cultures at Boston City Hospital between 1979 and 1982. J Infect Dis 1984; **149**: 449–52.
43. Butler J, Breiman R, Lipman H, Hofmann J, Facklam R. Serotype distribution of *Streptococcus pneumoniae* infections among preschool children in the United States, 1978–1994: implications for development of a conjugate vaccine. J Infect Dis 1995; **171**: 885–9.
44. Colman G, Cooke E, Cookson B, Cooper P, Efstratiou A, George R. Pneumococci causing invasive disease in Britain 1982–1990. J Med Microbiol 1998; **47**: 17–27.
45. Appelbaum P. Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. Clin Infect Dis 1992; **15**: 77–83.
46. Fedson DS. The clinical effectiveness of pneumococcal vaccination: a brief review. Vaccine 1999; **17**: S85–90.
47. Smart L, Dougall A, Girdwood R. New 23-valent pneumococcal vaccine in relation to pneumococcal serotypes in systemic and non-systemic. J Infect 1987; **14**: 209–15.
48. Johnson A, Speller D. Antibiotic resistance. Epidemiology of antibiotic resistance: blood and cerebrospinal fluid (CSF). J Med Microbiol 1997; **46**: 445–7.
49. Hedlund J, Stevenson S, Kalin M, et al. Incidence, capsular types, and antibiotic susceptibility of invasive *Streptococcus pneumoniae* in Sweden. Clin Infect Dis 1995; **21**: 948–53.
50. Lovgren M, Spika JS, Talbot JA. Invasive *Streptococcus pneumoniae* infections: serotype distribution and antimicrobial resistance in Canada, 1992–1995. Can Med Assoc J 1998; **158**: 327–31.
51. Jamal F. Epidemiological data on pneumococcal infections in Asian countries. Vaccine 1999; **17**: S75–8.
52. Lee C. Bacterial capsular polysaccharide – biochemistry, immunity and vaccine. Mol Immunol 1987; **24**: 1005.
53. Greenwood B. The epidemiology of pneumococcal infection in children in the developed world. Phil Trans R Soc Lond B 1999; **354**: 777–85.
54. Mbelle N, Huebner RE, Wasas AD, et al. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis 1999; **180**: 1171–6.
55. Obaro S, Adegbola R, Banya W, Greenwood B. Carriage of pneumococci after pneumococcal vaccine. Lancet 1996; **348**: 271–2.
56. Dagan R, Melamed R, Muallem M, et al. Reduction of nasopharyngeal carriage of pneumococci during the second year of life by a heptavalent conjugate pneumococcal vaccine. J Infect Dis 1996; **174**: 1271–8.
57. Hausdorff WP, Bryant J, Kloek C, Paradiso PR, Siber GR. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, part II. Clin Infect Dis 2000; **30**: 122–40.
58. Klein D. Pneumococcal conjugate vaccines: review and update. Microb Drug Resist 1995; **1**: 49–58.
59. Klugman K. Pneumococcal resistance to antibiotics. Clin Microbiol Rev 1990; **3**: 171–96.
60. Tomasz A. Antibiotic resistance in *Streptococcus pneumoniae*. Clin Infect Dis 1997; **24** (Suppl): S85–8.
61. Klugman K, Koornhof H. Drug resistance patterns and

serogroups or serotypes of pneumococcal isolates from cerebrospinal fluid or blood, 1979–1986. J Infect Dis 1988; **158**: 956–64.

62. Ridgway E, Allen K, Galloway A, Rigby A, Donoghue O. Penicillin-resistance pneumococci in a Merseyside hospital. J Hosp Infect 1991; **17**: 15–23.
63. George R, Ball L, Cooper P. Antimicrobial-resistant pneumococci in the United Kingdom. CDR 1992; **2**: R37–43.
64. Boswell T, Frodsham D, Nye K, Smith E. Antibiotic resistance and serotypes of *Streptococcus pneumoniae* at Birmingham Public Health Laboratory, 1989–1994. J Infect 1996; **33**: 17–22.
65. Jette L, Ringuette L, Dascal A, Lapointe J. Pneumococcal resistance to antimicrobial agents in the province of Quebec, Canada. J Clin Microbiol 1994; **32**: 2572–5.
66. Hofmann J, Cetron M, Farley M, et al. The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. NEJM 1995; **333**: 481–6.
67. Coffey T, Berron S, Daniels M, et al. Multiply-antibiotic-resistant *Streptococcus pneumoniae* recovered from Spanish hospitals (1988–1994): novel major clones of serotypes 14, 19F and 15F. Microbiol 1996; **142**: 2747–57.
68. Paul J, Kimari J, Gilks C. Serotypes and antibiotics susceptibilities of *Streptococcus pneumoniae* in Nairobi, Kenya. J Infect Dis 1996; **32**: 139–42.
69. Scott J, Hall A, Hannington A, et al. Serotype distribution and prevalence of resistance to benzylpenicillin in three representative populations of *Streptococcus pneumoniae* isolates from the coast of Kenya. J Infect Dis 1998; **27**: 1442–50.

Epidemiol. Infect. (2002), **128**, 139–147. © 2002 Cambridge University Press
DOI: 10.1017/S0950268801006586 Printed in the United Kingdom

Incidence of invasive pneumococcal disease in Scotland, 1988–99

M. H. KYAW[1,3]*, S. CLARKE[2], I. G. JONES[3] AND H. CAMPBELL[1]

[1] *University of Edinburgh, Public Health Sciences, Edinburgh*
[2] *Scottish Meningococcus and Pneumococcus Reference Laboratory, Glasgow*
[3] *Scottish Centre for Infection and Environmental Health, Glasgow*

(*Accepted 22 October 2001*)

SUMMARY

A review of the epidemiology of invasive pneumococcal disease in Scotland was carried out using data from laboratory-based systems during the period 1988–99. This comprised 5456 (90·8%) isolates of *Streptococcus pneumoniae* from blood, 467 (7·8%) from cerebrospinal fluid (CSF) and 84 (1·4%) from other sterile sites. The mean annual incidence of invasive disease was $9{\cdot}8/10^5$ population ($9{\cdot}0/10^5$ for bacteraemia and $0{\cdot}8/10^5$ for meningitis). Invasive disease was highest in children < 2 years of age and in the elderly $\geqslant 65$ years ($44{\cdot}9/10^5$ and $28{\cdot}4/10^5$ population in these age groups respectively). The highest incidence of pneumococcal meningitis, $11{\cdot}8/10^5$ persons occurred in children < 2 years of age. Males had a higher incidence of pneumococcal bacteraemia and meningitis than females (male:female = 1·2:1 for bacteraemia (RR = 1·17, 95% CI 1·11, 1·24) and 1·5:1 for meningitis (RR = 1·41, 95% CI 1·18, 1·70)). Pneumococcal disease was highest in winter periods and coincided with influenza activity. The proportion of penicillin and erythromycin non-susceptible isolates increased from 4·2% in 1992 to 12·6% in 1999 and from 5·6% in 1994 to 16·3% in 1999 respectively. Our data confirm the substantial and increasing disease burden from pneumococcal disease and rise in prevalence of antibiotic non-susceptibility among pneumococci in Scotland. Continued surveillance of groups at increased risk for pneumococcal disease and the antibiotic susceptibility and serotype distribution of isolates are important to develop appropriate policies for the prevention of pneumococcal disease in Scotland.

INTRODUCTION

Streptococcus pneumoniae is one of the leading causes of bacteraemia and meningitis in the United Kingdom. The incidence of invasive pneumococcal disease is greatest in young children, the elderly and persons with underlying medical conditions which place them at increased risk [1]. Despite the use of appropriate antimicrobial agents, case fatality rates of 12–38% have been documented in high-risk groups [2–4] and the emergence of antimicrobial resistant pneumococci has been noted globally [5]. Although it is not consistently documented [6], there is strong evidence that penicillin resistant invasive pneumococcal strains are associated with increased morbidity and mortality rates [2, 4]. These data clearly highlight the clinical impact and economic burden of pneumococcal disease and the need to prevent it by vaccination.

This paper reports on all invasive pneumococcal isolates referred to reference laboratories in Scotland during the period 1988–99 and examines the epidemio-

* Author for correspondence: Scottish Centre for Infection and Environmental Health, Clifton House, Clifton Place, Glasgow, G3 7LN.

logical characteristics of invasive pneumococcal disease. These data should inform future vaccination policy in Scotland.

Background and study data

Analyses were performed on a combined dataset from the Scottish Centre for Infection and Environmental Health (SCIEH) and Scottish Meningococcus and Pneumococcus Reference Laboratory (SMPRL). Detailed background information was given in a previous report [7] which documented the serotypes/groups distribution and coverage of polysaccharide and conjugate vaccines in different age groups. Information on antibiotic prescriptions for penicillin and erythromycin in Scotland between 1992 and 1999 was obtained from the Primary Care Unit, Information and Statistics Division of the NHS in Scotland. Pneumococcal isolates that had minimal inhibitory concentration (MIC) values to penicillin $< 0{\cdot}06\ \mu g/ml$, between $0{\cdot}12$ and $1{\cdot}0\ \mu g/ml$ and $2{\cdot}0\ \mu g/ml$ or higher were defined as susceptible, intermediate resistant and resistant respectively. The latter two categories were considered non-susceptible to penicillin. For erythromycin a single breakpoint concentration ($1\ \mu g/ml$) was used to differentiate between susceptible and resistant isolates. MICs were determined by a standard agar dilution method (incorporating the antibiotic into agar) from 1992–3 and by the E-test (Cambridge Diagnostics, Cambridge UK) since 1994. A weekly review of laboratory reports is conducted by SCIEH to ensure the accuracy of records of pneumococcal disease. This showed in 1999 over 90% completeness for both reporting and organism submission for invasive pneumococcal disease. Between 1988 and 1999, the number of laboratories reporting pneumococcal infections to SCIEH and SMPRL increased from 29 to 33 and this increase occurred after 1994. The corresponding denominator population for reporting over this period rose from 5093000 to 5512000 [8]. The mid-point year (1993) population was used to calculate the age specific incidence rate.

Statistical analysis

Pearson correlation coefficients were used to determine associations between variables using SPSS version 8. Relative risk and corresponding 95% confidence intervals and the χ^2 test for trends were calculated using the CIA programme (Gardner SB, Winter PD, Gardner MJ: London, 1991).

RESULTS

A total of 17781 *S. pneumoniae* cases were identified in SCIEH and SMPRL databases. After removal of duplicate records, 10498 cases remained. Of these 6007 were invasive isolates; 5456 (90·8%) were from blood, 467 (7·8%) from CSF and 84 (1·4%) from other sterile sites.

Invasive pneumococcal isolates by age and sex

Of the 6007 invasive isolates, 2675 (44·5%), were from the elderly ($\geqslant 65$ years of age) and 734 (12·2%) were from children $\leqslant 5$ years of age, 2186 (36·4%) were from 6–64 age group and for 412 (6·9%) the age was unknown. The age range of patients was 0–99 years (median = 63, mean = 54). There were 2758 (45·9%) isolates from females and 3077 (51·2%) from males. Sex was not recorded in 172 (2·9%) records. Both the frequency and incidence of pneumococcal bacteraemia and meningitis were higher in males than females. The overall incidence in males and females was 9·4 and $8{\cdot}1/10^5$ population (male:female = 1·2:1) (RR = 1·17, 95% CI 1·11, 1·24) for bacteraemia and 0·9 and $0{\cdot}6/10^5$ population (male:female = 1·5:1) (RR = 1·41, 95% CI 1·18, 1·70) for meningitis.

Annual incidence

The mean annual incidence of invasive pneumococcal disease was $9{\cdot}8/10^5$ population from 1988 to 1999 and a gradual increase was observed over the study period. This was due to an increase in reported bacteraemia from 248 in 1988 to 510 in 1999. No increase in meningitis was noted. Bacteraemia increased in children $\leqslant 5$ years of age (26 in 1988 to 66 in 1999), and the elderly (114 in 1988 to 245 in 1999). In the last 6 years, the incidence of invasive pneumococcal disease has been relatively stable (Fig. 1). The annual incidences of bacteraemia and meningitis were higher in males than females during the period 1988–99 (except for years 1993 and 1996 for meningitis and 1994 for bacteraemia).

Age specific incidence of disease

Figure 2 shows that the incidence of invasive disease was highest in infants under 2 years of age and the

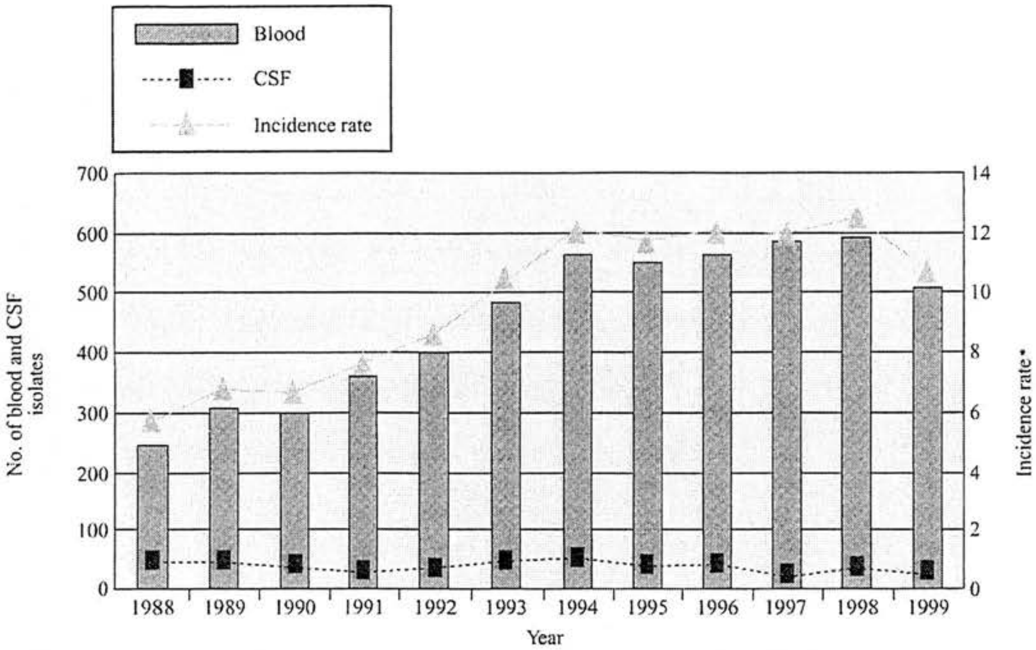


Fig. 1. Incidence of invasive pneumococcal disease (blood and CSF isolates), 1988–99. *Rate per 100000 population.

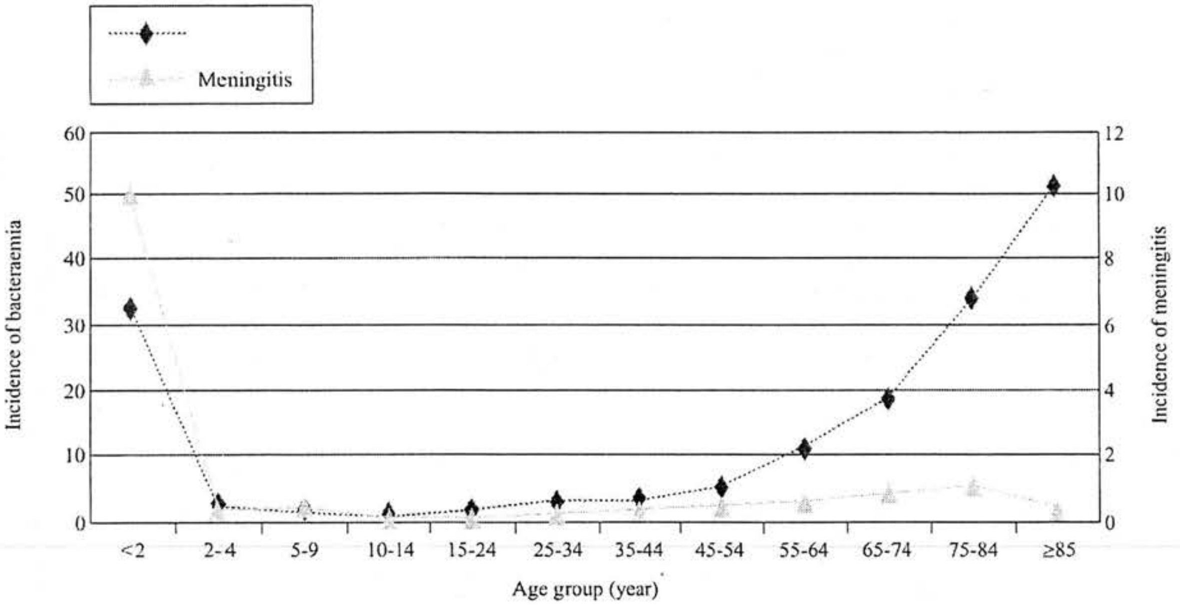


Fig. 2. Incidence of pneumococcal bacteraemia and meningitis per 100000 by age group, 1988–99.

elderly (44·9 and $28{\cdot}4/10^5$ population respectively). The rate for bacteraemia was $9/10^5$ population in all ages but reached $33{\cdot}1/10^5$ population in the youngest patients and $27{\cdot}5/10^5$ population in the oldest. The rise in bacteraemia in the study period was particularly marked in infants (16·9 in 1988 to $47{\cdot}4/10^5$ population in 1998) and the elderly (14·5 in 1988 to $31{\cdot}2/10^5$ population in 1999).

The rate of meningitis was $0{\cdot}8/10^5$ population in all ages. The highest incidence ($11{\cdot}8/10^5$ population) was in infants but this was significantly lower ($0{\cdot}4/10^5$ population) in the 2–4 years age group. There was no increase in pneumococcal meningitis over the study period 1988–99 (Fig. 1).

Seasonal variation

A significant seasonal variation in pneumococcal disease was observed. Data aggregated in 3-month periods over the study period showed that the number

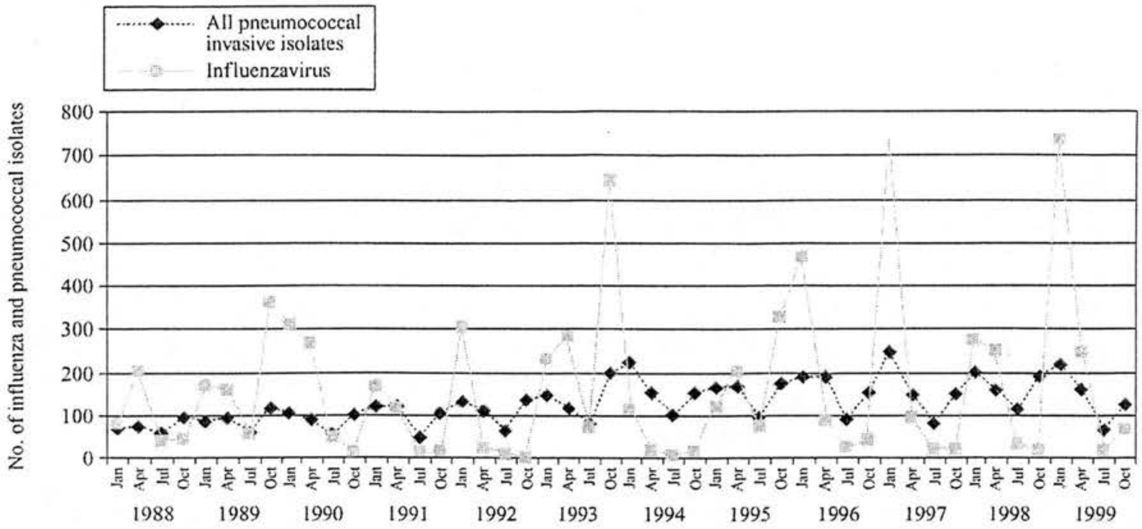


Fig. 3. Seasonal pattern of laboratory reports of influenza and invasive pneumococcal isolates by 3 months block, Scotland, 1988–99.

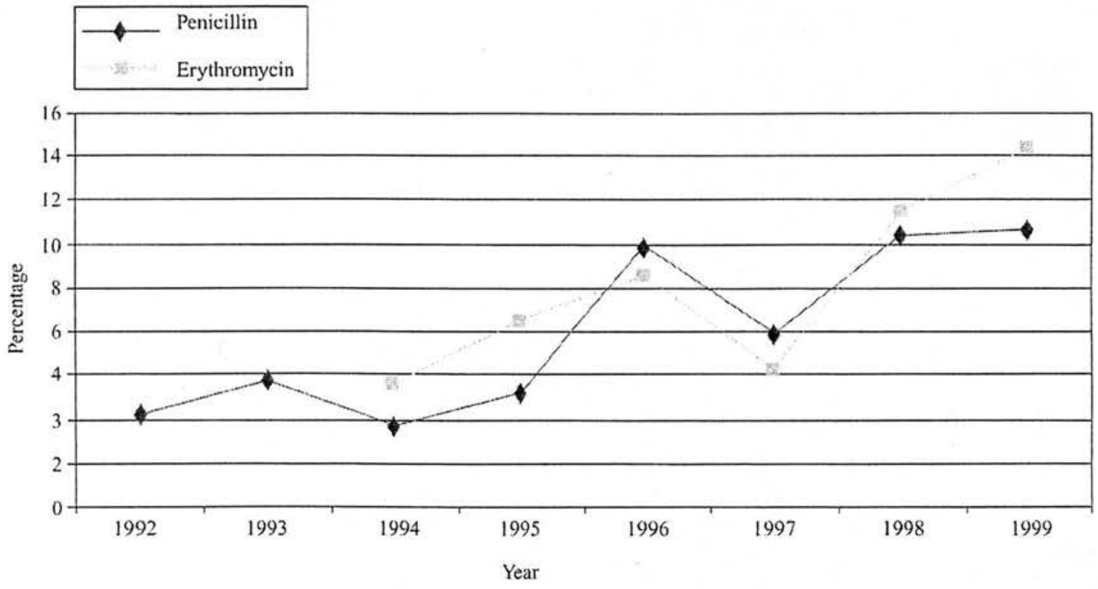


Fig. 4. Penicillin (1992–9) and erythromycin (1994–9) non-susceptible pneumococci in Scotland.

of cases peaked in the first 3 months of the year. This pattern was similar to that for influenza activity reported to SCIEH (Fig. 3).

Antimicrobial susceptibility

Of the 6007 invasive isolates, 1248 and 1053 were tested for penicillin and erythromycin MIC levels respectively and the great majority of them (87% and 95%) were fully susceptible to these antibiotics. Penicillin non-susceptible isolates increased from 1 (4·2%) in 1992 to 21 (12·6%) in 1999 (χ^2 for trend = 11·52, $P = 0{\cdot}0007$) (Fig. 4) and erythromycin resistant isolates from 7 (5·6%) in 1994 to 27 (16·3%) in 1999 ($P = 0{\cdot}0015$). Only 2 cases of penicillin-resistant pneumococci were reported (in 1998).

Antimicrobial susceptibility and antibiotic prescriptions

Scotland is divided geographically into 15 health board areas for administrative purposes. There was some geographical variation in penicillin and erythromycin non-susceptibility patterns of pneumococci (Table 1). A statistically significant correlation was recorded for penicillin prescription rate and the incidence of non-susceptible isolates in each health

Table 1. *Geographic variation in penicillin and erythromycin susceptibility and non-susceptibility of pneumococcal isolates and the patterns of penicillin and erythromycin prescriptions in Scotland.*

	Penicillin sensitivity (1992–9):* No. (%)				Rate (per year)		Erythromycin sensitivity (1994–9):‡ No. (%)			Rate (per year)	
Area	S	I	R	Total	Penicillin non-susceptible isolates†	Penicillin prescription (× 10^5)	S	R	Total	Erythromycin non-susceptible isolates§	Erythromycin prescription (× 10^5)
AC	41 (73·2)	15 (26·8)	0 (0)	56 (100)	0·4	24·6	50 (94·3)	3 (5·7)	53 (100)	0·1	5·9
AA	77 (91·7)	6 (7·1)	1 (1·2)	84 (100)	0·2	22·9	52 (89·7)	6 (10·3)	58 (100)	0·3	5·6
BR	12 (80)	2 (13·3)	1 (6·7)	15 (100)	0·4	21·2	6 (100)	0 (0)	6 (100)	0	5·6
DG	3 (30)	7 (70)	0 (0)	10 (100)	0·6	21·7	6 (75)	2 (25)	8 (100)	0·2	3·7
FF	7 (70)	3 (30)	0 (0)	10 (100)	0·1	23·5	8 (88·9)	1 (11·1)	9 (100)	0·1	6·1
FV	46 (93·9)	3 (6·1)	0 (0)	49 (100)	0·1	21·4	35 (89·7)	4 (10·3)	39 (100)	0·3	5·5
GR	10 (76·9)	3 (23·1)	0 (0)	13 (100)	0·1	22·1	5 (45·5)	6 (54·5)	11 (100)	0·2	6·4
GG	318 (87·1)	47 (12·9)	0 (0)	365 (100)	0·7	28	279 (91·5)	26 (8·5)	305 (100)	0·5	7·6
LN	221 (96·5)	8 (3·5)	0 (0)	229 (100)	0·2	27·6	178 (88·6)	23 (11·4)	201 (100)	0·7	7·3
LO	333 (97·7)	8 (2·3)	0 (0)	341 (100)	0·1	23·4	263 (90·4)	28 (9·6)	291 (100)	0·6	5·9
OR	0 (0)	0 (0)	0 (0)	0 (0)	0	20·7	0 (0)	0 (0)	0 (0)	0	5·4
SH	0 (0)	0 (0)	0 (0)	0 (0)	0	20·9	0 (0)	0 (0)	0 (0)	0	6·3
TY	25 (92·6)	2 (7·4)	0 (0)	27 (100)	0·1	23·8	21 (87·5)	3 (12·5)	24 (100)	0·1	5·7
WI	4 (100)	0 (0)	0 (0)	4 (100)	0	18·6	3 (75)	1 (25)	4 (100)	0·6	5·8
HG	42 (100)	0 (0)	0 (0)	42 (100)	0	21·4	37 (88·1)	5 (11·9)	42 (100)	0·4	5·6
Scotland	1139 (91·5)	104 (8·4)	2 (0·2)	1245 (100)	0·3	24·8	943 (89·7)	108 (10·3)	1051 (100)	0·4	6·3

S, sensitive; I, intermediate; R, resistance; *, 3 patients did not have area locations; †, resistant isolates, non-susceptible (intermediate and resistance); ‡, 2 patients did not have area locations; §, resistant isolates, non-susceptible, Rate = per 10^5 population per year.

AC, Argyll & Clyde; AA, Ayrshire & Arran; BR, Borders; DG, Dumfries & Galloway; FF, Fife; FV, Forth Valley; GG, Greater Glasgow; GR, Grampian; HG, Highland; LN, Lanarkshire; LO, Lothian; OR, Orkney; SH, Shetland; TY, Tayside; WI, Western Isles.

board (Pearson correlation, $r = 0{\cdot}52$, $P = 0{\cdot}047$). No correlation was documented for erythromycin prescription rate and the incidence of erythromycin non-susceptible isolates ($r = 0{\cdot}39$, $P = 0{\cdot}157$).

DISCUSSION

Contemporary population based data on the age and sex specific incidence of pneumococcal bacteraemia and meningitis in the United Kingdom are scarce. This may in part reflect a poor understanding of the public health burden of invasive pneumococcal disease. This study reports on invasive pneumococcal disease throughout Scotland in the years 1988–99 and is based on a large database of high quality data on pneumococcal isolates reported to SCIEH and SMPRL. Because acceptance criteria for the diagnosis of pneumococcal infections differ widely we included only laboratory confirmed cases of *S. pneumoniae* recovered from blood, CSF and other sterile sites.

The reported incidence of invasive pneumococcal disease varies widely between countries. Nevetheless, it is universally recognized that the elderly and young children are most at risk of bacteraemia [9], and those under 2 years, of meningitis [10, 11]. A higher incidence of invasive disease has been reported in native populations in New Zealand [12], Alaska (US) [13], Apache (US) [14], Navajo (US) [15] and Aboriginal (Australia) [16] compared with other population groups in the respective countries. Similarly high rates have been found in young children in Gambia [17, 18], Israel [19] and Chile [20]. Our data show a greater incidence of invasive pneumococcal disease in males (51%) than females (46%). This is consistent with previous studies from the United Kingdom [3], United States [21], Europe [22, 23], and Australian Aboriginals [16].

We found a twofold increase in incidence of invasive disease in Scotland over the period 1988–99 which is similar to that reported in most studies from the United States and Sweden [24, 25] but is different from Finland in the last decade [22]. In contrast to the twofold annual increase in bacteraemia, there was no increase in pneumococcal meningitis during the study period. The increase in bacteraemia may be an artifact due to an increase in the number of blood cultures taken rather than in disease incidence [26, 27] and changing referral practices by diagnostic laboratories may also have had an influence. Furthermore increased clinical awareness and patterns of investigations may also have affected the earlier rise in incidence. However, the participation of an additional four diagnostic laboratories from 1994 onwards is unlikely to explain most of the observed increase in disease incidence since a clear increased trend was established prior to that year.

Our data may still represent an underestimate of invasive disease since most febrile patients are not routinely tested by blood culture. Blood cultures also lack sensitivity for confirmation of pneumococcal disease [28] as only 10–20% of blood cultures are reported positive [29]. Although lung aspirates are more sensitive than blood cultures, the technique is not suitable for routine use [30] and may cause adverse effects [31]. Recently, a PCR method to detect pneumococcal DNA in blood has been shown to improve the diagnosis of bacteraemia [32]. The lack of a reliable diagnostic method may therefore contribute to an underestimate of the burden of pneumococcal disease [30]. Moreover, prior to antibiotic treatment blood culture confounds the diagnosis as a study demonstrated that only 5% of blood cultures were positive in those who had prior antibiotics compared with 19% in those who did not receive them [33].

The prevalence of invasive disease was clearly related to season in the present study with the highest reported cases in January–March each year which coincided with the period of peak influenza activity. Previous studies in the United Kingdom [3, 34], United States [35] and Israel [19] have also shown that pneumococci are isolated more frequently during the winter period. This seasonal increase may be influenced by the coincident circulation of other respiratory viruses as winter is associated with increased respiratory virus activity which has been cited as a risk factor for developing pneumococcal disease [35, 36]. About 50–80% of pneumococcal pneumonia is thought to be associated with prior occurrence of some form of viral respiratory illness [36].

In the present study, the proportion of both penicillin and erythromycin non-susceptible isolates increased by threefold. A gradual increase in the prevalence of drug resistance in *S. pneumoniae* has been documented worldwide [37, 38]. From 1990 to 1998, the PHLS Communicable Disease Surveillance Centre in England and Wales noted an increase from < 1% to 3·6–7·4% for penicillin resistant isolates and of 5% to 11% for erythromycin resistant isolates [39]. In the United States, the level of drug resistant pneumococci increased from 14% in 1993/4 [40] to 25% in 1998 [41]. Increased awareness of invasive disease and improved detection of resistant isolates by laboratories may also have contributed to this increase.

Penicillin resistance in isolates has serious implications for the management of invasive pneumococcal disease, particularly for meningitis. The clinical failure of third line generation antibiotics (cefotaxime/ceftriaxone or other cephalosporins) effective against penicillin-resistant strains has been documented [42, 43]. Experience in the United States demonstrates that outbreaks of pneumococcal meningitis with multi-drug resistant strains (serotype 14) can occur [44] and, indeed, invasive pneumococcal disease with penicillin-resistant strains has been associated with increased mortality rates [4] and longer periods of hospitalization [2].

Seroepidemiology data in the United Kingdom shows that the current 23-valent polysaccharide pneumococcal vaccine includes the majority of serotypes/groups that show resistance to many antibiotics [7, 45]. Thus, the increased use of these vaccines may serve to prevent invasive disease due to antimicrobial resistant strains in high-risk individuals. Seven to 11-valent pneumococcal conjugate vaccines have been reported to reduce nasopharyngeal carriage, particularly associated with drug resistant serotypes, in vaccinated children [46]. Our previous report showed that 7 to 11-valent conjugate vaccines cover > 94% of penicillin and 100% of erythromycin non-susceptible pneumococcal isolates in Scotland [7]. Therefore, the widespread use of conjugate vaccines has the potential to reduce the transmission of drug-resistant pneumococci. A 7-valent conjugate pneumococcal vaccine has been licensed for use in children in the United States. The decision on use of this new vaccine in the UK is expected soon.

We found variation in antibiotic non-susceptibility in different geographic locations in Scotland. The reasons for this may be complex but mobility of the population probably contributed to these differences [41, 47, 48]. Others have shown that the frequency of antibiotic resistant invasive pneumococcal isolates varies within and between countries [37, 38] with reported rates within the United States of 7–25% to penicillin and 6–15% to erythromycin [2, 49–51]. It has been suggested that variation in antibiotic use influences the prevalence of resistant strains of pneumococci in different locations [52]. Other factors such as differences in populations and different study methods may also play a part. Antibiotic prescription data indicated geographical variation in prescription rates for penicillin and erythromycin and a significant correlation with frequencies of antibiotic resistant strains of pneumococci was recorded for penicillin only, not erythromycin.

In conclusion, our data confirm the substantial and increasing public health burden from pneumococcal disease and the concomitant rise in antibiotic non-susceptibility among pneumococci in Scotland. It is clear that this burden cannot be eliminated by the utilization of antibiotics alone. Polysaccharide or new conjugate pneumococcal vaccines in high-risk individuals remain the most effective preventive measure to reduce disease and control the spread of resistant isolates. Continued surveillance of the incidence of pneumococcal disease, serotypes/groups distribution and antibiotic susceptibility continue to be essential to inform policy and decision making to reduce the burden to the public health.

ACKNOWLEDGEMENTS

We thank the laboratory staff throughout Scotland for reporting cases of pneumococcal infections to the Scottish Centre for Infection and Environmental Health and Scottish Meningococcus and Pneumococcus Reference Laboratory. We are also grateful to Dr Eileen Holmes for statistical advice.

REFERENCES

1. MMWR. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997: **46**: 1–24.
2. Plouffe JF, Breiman RF, Facklam RR, et al. Bacteremia with *Streptococcus pneumoniae*: implications for therapy and prevention. JAMA 1996; **275**: 194–8.
3. Laurichesse H, Grimaud O, Waight P, Johnson A, George R, Miller E. Pneumococcal bacteraemia and meningitis in England and Wales, 1993 to 1995. Commun Dis Pub Hlth 1998; **1**: 22–7.
4. Feikin DR, Schuchat A, Kolczak M, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance 1995–1997. Am J Pub Hlth 2000; **90**: 223–9.
5. Schreiber J, Jacobs M. Antibiotic-resistant pneumococci. Ped Clin N Am 1995; **42**: 519–37.
6. Moroney JF, Fiore AE, Harrison LH, et al. Clinical outcomes of bacteraemic pneumococcal pneumonia in the era of antibiotic resistance. Clin Infect Dis 2001; **33**: 797–805.
7. Kyaw MH, Clarke S, Edwards G, Jones IG, Campbell H. Serotypes/groups distribution and antimicrobial resistance of invasive pneumococcal isolates: implication for vaccine strategies. Epidemiol Infect 2000; **125**: 561–72.

8. Office for National Statistics. Monthly digest of statistics. No. 649. 2000 January. London: The Stationary Office, 2000.
9. Fedson D, Musher D, Eskola J. Pneumococcal vaccine. In: Plotkin SA, Orenstein WA, eds. Vaccines. Philadelphia: W. B. Saunders Co, 1999: 553–607.
10. Schuchat A, Robinson K, Wenger JD, et al. Bacterial meningitis in the United States in 1995. N Engl J Med 1997; **337**: 970–6.
11. Sleeman K, Knox K, George R, et al. Invasive pneumococcal disease in England and Wales: vaccination implications. J Infect Dis 2001; **183**: 239–46.
12. Voss L, Lennon D, Okesene-Gafa K, Ameratunga S, Martin D. Invasive pneumococcal disease in a pediatric population, Auckland, New Zealand. Pediatr Infect Dis J 1994; **13**: 873–8.
13. Davidson M, Parkinson A, Bulkow L, Fitzgerald M, Peters H, Parks D. The epidemiology of invasive pneumococcal disease in Alaska 1986–1990: ethnic differences and opportunities for prevention. J Infect Dis 1994; **170**: 368–76.
14. Cortese M, Wolff M, Almeido-Hill J, et al. High incidence rate of invasive pneumococcal disease in the White Mountain Apache population. Arch Intern Med 1992; **152**: 1–6.
15. Overturf GD. Technical report: prevention of pneumococcal infections, including the use of pneumococcal conjugate and polysaccharide vaccines and antibiotics prophylaxis. Pediatrics 2000; **106**: 367–76.
16. Torzillo PJ, Hanna JN, Morey F, Gratten M, Dixon J, Erlich J. Invasive pneumococcal disease in central Australia. Med J Aust 1995; **162**: 182–6.
17. O'Dempsey TJ, Mcardle TF, Lloyd-Evans N, et al. Pneumococcal disease among children in a rural area of West Africa. Pediatr Infect Dis J 1996; **15**: 431–7.
18. Usen S, Adegbola R, Mulholland K, et al. Epidemiology of invasive pneumococcal disease in the Western region, The Gambia. Pediatr Infect Dis J 1998; **17**: 23–8.
19. Dagan R, Englehard D, Piccard E, et al. Epidemiology of invasive childhood pneumococcal infections in Israel. JAMA 1992; **268**: 3328–32.
20. Levine MM, Lagos R, Levine OS, et al. Epidemiology of invasive pneumococcal infections in infants and young children in Metropolitan Santiago, Chile, a newly industrializing country. Pediatr Infect Dis J 1998; **17**: 287–93.
21. Nuorti JP, Butler JC, Gelling L, Kool JL, Reingold AL, Vugia DJ. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. Ann Intern Med 2000; **132**: 182–90.
22. Sankilampi U, Herva E, Haikala R, Liimatainen O, Renkonen O-V, Leinonen M. Epidemiology of invasive *Streptococcus pneumoniae* infections in adults in Finland. Epidemiol Infect 1997; **118**: 7–15.
23. Burman L, Norrby R, Trollfors B. Invasive pneumococcal infections: incidence, predisposing factors and prognosis. Rev Infect Dis 1985; **7**: 133–42.
24. Ortqvist A. Pneumococcal disease in Sweden: experiences and current situation. Am J Med 1999; **107** Suppl 1A: S44–S49.
25. Mufson MA, Stanek RJ. Bacteraemic pneumococcal pneumonia in one American city: a 20-year longitudinal study 1978–1997. Am J Med 1999; **107** Suppl 1A: S34–S43.
26. Breiman R, Spika J, Navarro V, Darden PM, Darby CP. Pneumococcal bacteremia in Charleston County, South Carolina a decade later. Arch Intern Med 1990; **150**: 1401–5.
27. Nielsen S, Henrichsen J. Incidence of invasive pneumococcal disease and distribution of capsular types of pneumococci in Denmark, 1989–1994. Epidemiol Infect 1996; **117**: 411–6.
28. Korppi M, Koskela M, Jalonen E, Leinonen M. Serologically indicated pneumococcal respiratory infection in children. Scand J Infect Dis 1992; **24**: 437–43.
29. Greenwood B. The epidemiology of pneumococcal infection in children in the developed world. Phil Trans R Soc Lond B 1999; **354**: 777–85.
30. Shann F. Etiology of severe pneumonia in children in developing countries. Pediatr Infect Dis J 1986; **5**: 247–52.
31. Adegbola R, Falade A, Sam B, et al. The aetiology of pneumonia in malnourished and well-nourished Gambian children. Pediatr Infect Dis J 1994; **13**: 975–82.
32. Porath A, Schlaeffer F, Lieberman D. The epidemiology of community-acquired pneumonia among hospitalised adults. J Infect 1997; **34**: 41–8.
33. Lim I, Shaw D, Stanley D, et al. A prospective hospital study of the etiology of community-acquired pneumonia. Med J Aust 1989; **151**: 87–91.
34. Smith M, Stuart J, Andrews N, et al. Invasive pneumococcal infection in South and West England. Epidemiol Infect 1998; **120**: 117–23.
35. Kim PE, Musher DM, Glezen WP, Rodriguez-Barradas M, Nahm W, Wright C. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution and the isolation of respiratory viruses. Clinic Infect Dis 1996; **22**: 100–6.
36. Heffron R Pneumonia with special reference to pneumococcal lobar pneumonia. Cambridge, MA: Harvard University Press, 1979.
37. Forward KR. The epidemiology of penicillin resistance in *Streptococcus pneumoniae*. Semin Resp Infect 1999; **14**: 243–54.
38. Collignon PJ, Turnidge JD. Antibiotic resistance in *Streptococcus pneumoniae*. Med J Aust 2000; **173** Suppl: S58–S64.
39. Reacher MH, Shah A, Livermore DM, et al. Bacteraemia and antibiotic resistance of its pathogens reported in England and Wales between 1990 and 1998: trend analysis. BMJ 2000; **320**: 213–6.
40. Butler J, Hofmann J, Cetron M, Elliott J, Facklam R, Breiman R. The continued emergence of drug-resistant *Streptococcus pneumoniae* in the United States: an update from the Centres for Disease Control and

Prevention's Pneumococcal Sentinel System. J Infect Dis 1996; **174**: 986–93.

41. Whitney CG, Farley MM, Hadler J, et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. N Engl J Med 2000; **343**: 1917–24.
42. Bardley J, Connor J. Ceftriaxone failure in meningitis caused by *Streptococcus pneumoniae* with reduced susceptibility to beta-lactam antibiotics. Pediatr Infect Dis J 1991; **10**: 871–3.
43. Sloas M, Barrett F, Chesney P, et al. Cephalosporin treatment failure in penicillin-and cephalosporin-resistant *Streptococcus pneumoniae* meningitis. Pediatr Infect Dis J 1992; **11**: 662–6.
44. Craig AS, Erwin PC, Schaaffner W, et al. Carriage of multi-resistant *Streptococcus pneumoniae* and impact of chemoprophylaxis during an outbreak of meningitis at a day care center. Clin Infect Dis 1999; **29**: 1257–64.
45. Johnson AP, Speller DCE, George RC, et al. Prevalence of antibiotic resistance and serotypes in pneumococci in England and Wales: results of observational surveys in 1990 and 1995. BMJ 1996; **312**: 1454–6.
46. Dagan R, Fraser D. Conjugate pneumococcal vaccine and antibiotic resistant *Streptococcus pneumoniae* and reduction of otitis morbidity. Pediatr Infect Dis J 2000; **19** Suppl: S79–S88.
47. Soares S, Kristinsson K, Musser J, Tomasz A. Evidence for the introduction of a multi-resistant clone of serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the late 1980s. J Infect Dis 1993; **168**: 158–63.
48. Doern GV, Brueggemann AB, Huynh H, Wingert E, Rhomberg P. Antimicrobial resistance with *Streptococcus pneumoniae* in the United States 1997–98. Emerg Infect Dis 1999; **5**: 757–65.
49. Breiman R, Butler J, Tenover F, et al. Emergence of drug resistant pneumococcal infections in the United States. JAMA 1994; **271**: 1831–5.
50. Hofmann J, Cetron M, Farley M, et al. The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. N Engl J Med 1995; **333**: 481–6.
51. Metlay JP, Hofmann J, Cetron MS, et al. Impact of penicillin susceptibility on medical outcomes for adult patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2000; **30**: 520–528.
52. Arason V, Kristinsson K, Sigurdsson J, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? BMJ 1996; **17**: 387–91.

Epidemiol. Infect. (2002), **128**, 21–27. © 2002 Cambridge University Press
DOI: 10.1017/S0950268801006331 Printed in the United Kingdom

Non-invasive pneumococcal disease and antimicrobial resistance: vaccine implications

M. H. KYAW[1,3]*, S. CLARKE[2], I. G. JONES[3] AND H. CAMPBELL[1]

[1] *University of Edinburgh, Public Health Sciences, Edinburgh*
[2] *Scottish Meningococcus and Pneumococcus Reference Laboratory, Glasgow*
[3] *Scottish Centre for Infection and Environmental Health, Glasgow*

(*Accepted 30 September 2001*)

SUMMARY

We reviewed laboratory data on non-invasive pneumococcal isolates reported from all diagnostic laboratories in Scotland during the period 1988–99. Of 4491 isolates from hospitalized patients, 654 (64·7%) were from sputum, 79 (7·8%) from the nasopharynx and 278 (27·5%) from other superficial sites. The serogroups included in the 23-valent polysaccharide vaccine caused 96–9% of all non-invasive disease in all age groups. The 7-, 9-, and 11-valent conjugated vaccine serogroups were responsible for 87–94%, 85–93%, 74–81% and 75–84% of non-invasive disease respectively in age groups < 2 years, ⩽ 5 years, ⩾ 65 years and all ages. The coverage of non-susceptible penicillin and erythromycin non-invasive isolates was > 99% and > 95% with the 23-valent polysaccharide and 7–11-valent conjugate vaccines respectively. The eight most common serogroups were 23, 9, 6, 19, 14, 3, 15 and 11 (in descending order). The serogroups associated with antimicrobial resistance in non-invasive disease were similar to those found in invasive disease. The finding of a similar serogroup distribution in both invasive and non-invasive disease (regardless of the site of clinical isolate), is consistent with serogroups colonizing non-sterile sites and having the potential to invade. The availability of conjugated vaccines reinforces the importance of systematic surveillance to determine accurately and regularly the coverage of pneumococcal serogroups and types causing both invasive and non-invasive disease.

INTRODUCTION

The pneumococcus is a major pathogen in the young and the elderly and in those with underlying chronic medical disorders [1]. In addition, it is a leading cause of non-invasive diseases such as community-acquired pneumonia [2] and otitis media [3], and can be associated with considerable morbidity and economic burden [4]. It poses an important public health problem in the UK.

Although there are 90 known serotypes of pneumococci, the majority of pneumococcal disease is associated with fewer than 11 serotypes in infants and children and fewer than 23 serotypes in adults [5–7]. Colonization with pneumococcal serogroups 6, 14, 19 and 23 is most common in young children and adults [8–10]. These serogroups are also the dominant cause of disease and antibiotic resistance worldwide [11–14]. The available evidence shows that pneumococcal conjugated vaccines induce mucosal immunity [15]. Studies in South Africa and Israel showed a reduction in carriage of vaccine-related pneumococcal serotypes, especially antibiotic resistant strains [16, 17]. Thus, widespread use of pneumococcal conjugate vaccine could limit the spread of pneumococci and decrease the prevalence of antibiotic resistant strains.

Knowledge of the coverage of non-invasive sero-

* Author for correspondence: Scottish Centre for Infection and Environmental Health, Clifton House, Clifton Place, Glasgow, G3 7LN.

groups for 7–11-valent conjugated vaccines and the 23-valent pneumococcal polysaccharide vaccine in various age groups and from different clinical sites is important for vaccine formulation and recommendations for usage. In addition, data on the distribution of pneumococcal serogroups isolated from non-sterile site specimens may help to determine which serogroups are important in the development of invasive disease. We report here the prevalence of the major serogroups causing non-invasive disease and the coverage of polysaccharide and conjugated vaccines for non-invasive pneumococcal serogroups from population-based laboratory surveillance in Scotland, during the period 1988–99.

METHODS

Data from this study were obtained from the Scottish Centre for Infection and Environmental Health (SCIEH) and the Scottish Meningococcus and Pneumococcus Reference Laboratory (SMPRL). Both organizations provide the national surveillance and monitoring for diseases caused by these organisms in Scotland (estimated 5 million population). The establishment of SMPRL in 1992 has improved the data on both invasive and non-invasive pneumococcal disease, particularly for serogroup/type distribution and antimicrobial resistance in Scotland. Although SMPRL encourages all diagnostic laboratories to send isolates from body fluid of patients with suspected pneumococcal infection, it is likely that some laboratories may refer isolates thought to be antimicrobial resistant. Enhanced pneumococcal surveillance is currently underway in Scotland and will improve population-based data on this disease before and after the implementation of any pneumococcal conjugate vaccine strategy. Detailed background information and methods of this study have been described in a previous report [18]. This earlier study evaluated the prevalence of antibiotic resistance, serogroup/type distribution, and coverage of polysaccharide and conjugate pneumococcal vaccines related-serotypes/groups for invasive isolates. This report encompasses isolates from non-sterile sites from patients who were admitted to hospital mainly with acute respiratory infections and who were diagnosed as having pneumococcal infection. Serogrouping and serotyping of pneumococcal isolates were performed by coagglutination testing [19], using antisera obtained from the Statens Serum Institut (Copenhagen, Denmark). Isolates included those from sputum, nasopharynx, ear, eye, urine and other non-sterile sites. Antimicrobial susceptibility testing against penicillin and erythromycin was performed on selected isolates using the E-test method (Cambridge Diagnostics, Cambridge, UK). Isolates showing minimum inhibitory concentrations (MICs) of $\leqslant 0{\cdot}06\ \mu g/ml$, $0{\cdot}1$–$1\ \mu g/ml$ and $\geqslant 2\ \mu g/ml$ were considered sensitive, intermediate and highly resistant respectively, to penicillin. Erythromycin sensitivity and resistance were defined by MICs of $< 1\ \mu g/ml$ and $> 1\ \mu g/ml$ respectively. Intermediate resistant and highly resistant isolates were considered as non-susceptible isolates. Multiple isolates from the same patient were excluded from the study. Laboratory reports included demographic and limited clinical information. Data analysis was performed using SPSS version 10.

RESULTS

There was a total of 4491 non-invasive isolates in 1988–99. Of these, 1262 (28·1 %) were from females, 1692 (37·7 %) from males and in 1537 (34·2 %) cases, the patient gender was unknown. Serological information was available for 1011 (22·5 %) isolates. Of these serogrouped/typed isolates, 654 (64·7 %) isolates were from sputum, 79 (7·8 %) from the nasopharynx and 278 (27·5 %) from other non-invasive sites. Serogroup/type information was available for 186 (18·4 %) isolates from those aged less than 2 years, 209 (20·7 %) isolates from those aged 5 years or less, and 375 (37·1 %) isolates from those aged 65 years or more. Of the 1011 isolates with serological information, 524 had specific serotype information and 833 had serogroup information (Table 1).

Patient ages ranged from 1 year to 99 years, with a mean and median age of 36 years and 35 years respectively. Susceptibility to penicillin and erythromycin was tested in 60·4 % (611/1011) and 50 % (505/1011) of all isolates which were serogrouped/typed. The prevalence of non-susceptible isolates was 373/611 (61 %) for penicillin in 1992–9 and 70/505 (14 %) for erythromycin in 1994–9 for the isolates for which there was serogroup/type information.

Potential vaccine coverage in different age groups

Serogroups contained in the 23-valent vaccine accounted for 99 % of non-invasive isolates in age groups

Table 1. *Distribution of pneumococcal serotypes and serogroups*

	No.	Percent		No.	Percent
Serogroups			**Serotypes** (*cont.*)		
Groups			Types		
23	224	26·9	27	3	0·6
9	166	19·9	29	3	0·6
6	150	18	4	2	0·4
19	138	16·6	20	2	0·4
15	36	4·3	22A	2	0·4
11	35	4·2	34	2	0·4
33	18	2·2	42	2	0·4
7	15	1·8	5	1	0·2
10	15	1·8	16F	1	0·2
18	13	1·6	24F	1	0·2
17	6	0·7	37	1	0·2
12	5	0·6	Total	524	100
16	5	0·6			
22	3	0·4	**Serogroups/types**		
24	3	0·4	Groups/types		
41	1	0·1	23	224	22·2
Total	833	100	9	166	16·4
			6	150	14·8
Serotypes			19	138	13·6
Types			14	69	6·8
23F	77	14·7	3	54	5·3
23A	12	2·3	15	36	3·6
19F	57	10·9	11	35	3·5
19A	18	3·4	33	18	1·8
14	69	13·2	7	15	1·5
6A	32	6·1	10	15	1·5
6B	30	5·7	8	13	1·3
9V	36	6·9	18	13	1·3
9N	13	2·5	1	12	1·2
15B	16	3·1	35	9	0·9
15C	6	1·1	17	6	0·6
15A	3	0·6	12	5	0·5
15F	3	0·6	16	5	0·5
11A	33	6·3	31	5	0·5
11C	1	0·2	22	3	0·3
33F	16	3·1	24	3	0·3
10A	14	2·7	27	3	0·3
8	13	2·5	29	3	0·3
1	12	2·3	4	2	0·2
18C	12	2·3	20	2	0·2
7F	9	1·7	34	2	0·2
7C	1	0·2	42	2	0·2
35	7	1·3	5	1	0·1
17F	6	1·1	37	1	0·1
31	5	1	41	1	0·1
12F	3	0·6	Total	1011	100

< 2 years and ⩽ 5 years and 96% in age groups ⩾ 65 years and all ages. The coverage of 7, 9 and 11-valent conjugate vaccine in these age groups was 87–94%, 85–93%, 74–81% and 75–84% of non-invasive isolates respectively. Overall, coverage of 7- to 11-valent conjugate vaccine serogroups was between 85% and 94% for age groups < 2 years and ⩽ 5 years but their coverage reduced to 74–84% in age groups ⩾ 65 years and all ages. Overall, the 23-valent polysaccharide vaccine serogroups accounted

Table 2. *Coverage of pneumococcal vaccines for penicillin and erythromycin susceptible and non-susceptible isolates*

	Penicillin*				Erythromycin†		
	No. (%) of vaccine related serotype				No. (%) of vaccine related serotype		
Vaccine	Sensitive	Intermediate	Resistant	Total	Sensitive	Resistant	Total
7-valent	158 (66·4)	347 (95·6)	10 (100)	515 (84·3)	376 (86·4)	68 (97·1)	444 (87·9)
9-valent	166 (69·7)	348 (95·9)	10 (100)	524 (85·8)	382 (87·8)	68 (97·1)	450 (89·1)
11-valent	194 (81·5)	353 (97·2)	10 (100)	557 (91·2)	405 (93·1)	68 (97·1)	473 (93·7)
23-valent	228 (95·8)	360 (99·2)	10 (100)	598 (97·9)	423 (97·2)	70 (100)	493 (97·6)
Overall	238 (100)	363 (100)	10 (100)	611 (100)	435 (100)	70 (100)	505 (100)

* Sensitive MIC $\leqslant 0{\cdot}06$ μg/ml, intermediate MIC $0{\cdot}12$–$1{\cdot}0$ μg/ml, resistant MIC $\geqslant 2$ μg/ml, † Sensitive MIC < 1 μg/ml, resistant MIC > 1 μg/ml (7-valent vaccine serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F), (9-valent vaccine serotypes: 7-valent vaccine serotypes with serotypes 1 and 5), (11-valent vaccine serotypes: 9-valent vaccine serotypes with serotypes 3 and 7F), (23-valent vaccine serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F).

Table 3. *Penicillin and erythromycin susceptible and non-susceptible non-invasive pneumococcal serogroups/types*

	No. (%) of isolates						
	Penicillin				Erythromycin		
Serogroups/ types	Sensitive (MIC $\leqslant 0{\cdot}06$)	Intermediate (MIC = ($0{\cdot}12$–$1{\cdot}0$))	Resistance (MIC $\geqslant 2$)	Total	Sensitive (MIC < 1)	Resistance (MIC > 1)	Total
23	72	78	5	155	110	24	134
9	14	115	4	133	113	5	118
6	24	61	0	85	53	19	72
19	35	45	0	80	55	8	63
14	12	46	1	59	43	11	54
Others*	81	18	0	99	61	3	64
Total†	157 (66)	345 (95)	10 (100)	512 (83·8)	374 (86)	67 (95·7)	441 (87·3)
Total‡	238 (100)	363 (100)	10 (100)	611 (100)	435 (100)	70 (100)	505 (100)

* Others (sensitive = serogroups/types 11, 15, 1, 7, 10, 31, 33, 16, 4, 5, 22, 24, 29, 34, 35, 42) (intermediate = serogroups/types 8, 15, 7, 29, 1, 4, 18, 35) in descending order for penicillin. * Others (sensitive = serogroups/types 8, 15, 1, 7, 29, 31, 16, 4, 5, 18, 22, 24, 33, 34, 35, 42) (resistant = serogroups/types 4, 11, 15) in descending order for erythromycin. Non-susceptible isolates = intermediate and resistant isolates.

† Total isolates for serogroups/types (23, 9, 6, 19, 14).

‡ Overall total isolates.

for 96–9% of non-invasive disease respectively in all age groups.

Potential vaccine coverage for penicillin and erythromycin non-susceptible isolates

7–9-, 11-valent vaccine

The 7–11-valent vaccine serogroups accounted for > 95% and > 97% of penicillin and erythromycin non-susceptible non-invasive isolates respectively (Table 2).

23-valent vaccine

The coverage for non-susceptible penicillin and erythromycin non-invasive isolates was > 99% and 95% respectively with 23-valent vaccine (Table 2).

Most prevalent non-invasive pneumococcal serogroups, 1988–99

The eight most prevalent pneumococcal serogroups (in descending rank order) were 23, 9, 6, 19, 14, 3, 15 and 11. These eight serogroups were responsible for over 86·3% of non-invasive disease regardless of specimen type.

Antibiotic susceptibility

Serogroups 23, 9, 6, 19 and 14 were associated with the majority of penicillin and erythromycin non-susceptibility (Table 3).

DISCUSSION

Our data indicate that the serogroups included in the 23-valent polysaccharide and 7–11-valent conjugated pneumococcal vaccines caused the majority of non-invasive pneumococcal disease in all age groups in the study period in Scotland. In addition, serogroups associated with antibiotic resistance were found to be very similar in both non-invasive and invasive disease in Scotland [18]. In this study, data on coverage of vaccines were based on serogroups, assuming that there is cross-reactivity of serotype-specific protection within a serogroup (e.g. 6A *vs.* 6B, 9A *vs.* 9V) [20]. However, since there are limited data on cross-reactivity of vaccine serotypes within a serogroup [21], our data may have overestimated the potential coverage of vaccines for non-invasive disease. Penicillin resistant isolates are likely to be over-represented in this as a result of selectively higher referral by diagnostic laboratories. Also, only 60% and 50% of the total serogrouped/typed isolates were tested for penicillin and erythromycin susceptibility respectively in the study period. For these two reasons, data on antibiotic sensitivity should be interpreted with considerable caution.

Serogroups 23, 9, 6 and 19 were the predominant causes of non-invasive pneumococcal diseases, in keeping with earlier reports from the United Kingdom [22–4] and from other developed and developing countries [12, 25]. In common with other reports [12, 26], the coverage of 7–9-valent conjugated vaccine serogroups was lower for the elderly and the 'all age' group than the age groups < 2 years and $\leqslant 5$ years. The conjugated vaccine-related serogroups were the cause of over 80% of non-invasive disease in children under 2 years of age. Earlier studies [27, 28] reported a higher nasopharyngeal carriage with both vaccine serotypes and non-vaccine serotypes than in adults. Since there is an association between carriage and the spread of disease, children may be a major source of pneumococci and pneumococcal disease in the community. If so, universal vaccination of young children may extend protection from pneumococcal disease to non-vaccinated individuals by herd immunity.

The finding of a similar serogroup distribution in both invasive and non-invasive disease (regardless of the site of clinical isolate), is consistent with serogroups colonizing non-sterile sites and having the potential to cause invasive disease. Acquisition and carriage of *S. pneumoniae* is associated with the development of both invasive and non-invasive disease [28–30]. Data from Papua New Guinea suggest that serogroups/types causing upper respiratory tract infection (URTI) could be used to obtain a conservative estimate of susceptibility to invasive pneumococci [31]. Therefore, targeting vaccination on serogroups/types associated with non-invasive disease could reduce the risk of invasive disease. The efficacy of 7-valent pneumococcal conjugated vaccines in preventing pneumonia and otitis media has been documented: 73% (95% CI 38–88) against clinically diagnosed pneumonia confirmed with chest radiograph (pulmonary consolidation $\geqslant 2{\cdot}5$ cm) in a US study [32] and 57% (95% CI 44–67) against otitis media caused by vaccine serotypes in a Finnish study [33]. Studies from Europe and the United States reported that the estimated incidence rate of pneumococcal pneumonia was 5–9 per 1000 children under 5 years of age [34–36]. In addition, the incidence rate of pneumococcal otitis media has been estimated at 0·56 episodes per child under 2 years of age [3, 37]. Therefore, it appears that pneumococcal conjugated vaccination could reduce non-invasive disease caused by *S. pneumoniae* significantly. Additional studies are required to determine its efficacy in preventing disease in adults, the elderly and in immunocompromised patients.

Pneumococci carried in the upper respiratory tract are more often resistant to antibiotics than invasive strains [23, 38]. Serogroups 23 and 9 were frequently associated with penicillin and erythromycin non-susceptibility in this study. Our previous study on invasive pneumococcal isolates found that serotype 14 was the most common serotype associated with penicillin and erythromycin non-susceptibility [18]. In accordance with data from other countries [11], we found that serogroups 23, 9, 6, 19 and 14 were responsible for $\geqslant 95$% of non-invasive pneumococcal antibiotic resistance in Scotland. All these serogroups are represented in the 7-valent conjugated vaccine. Existing data suggest a reduction of antibiotic resistant pneumococcal serotypes [17] and use of antibiotics (5·3%) in pneumococcal conjugated vaccine recipients [39]. Thus, widespread use of pneumococcal conjugated vaccine could prevent the spread of antibiotic resistant pneumococcal isolates and thereby reduce antibiotic consumption. However, serotype exchange and capsular switching by pneumococci leading to an increase in virulence has been observed [40, 41]. It is possible that in the future, conjugated vaccine-induced pressure could lead to replacement of vaccine serotypes with non-vaccine serotypes of increased virulence, leading to increased disease and antibiotic resistance [42, 43]. Thus, it will be necessary to monitor the epidemiological, microbiological and immunological characteristics of the pneumococcal population worldwide. Our data highlight the importance of improved pneumococcal surveillance in Scotland in order to inform effective local public health strategies.

ACKNOWLEDGEMENTS

We thank the staff at microbiology laboratories and the Scottish Centre for Infection and Environmental Health for reporting and entering the data. We also thank Dr Peter Christie for helpful discussion and two reviewers for helpful comments. We are also grateful to Professor K. A. V. Cartwright for careful editing of the paper.

REFERENCES

1. Anonymous. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997; **46**: 1–24.
2. MacFarlane J. The clinical impact of pneumococcal disease. In: Mayon-White RT, ed. The clinical impact of pneumococcal disease and strategies for its prevention. Royal Society of Medicine International Congress and Symposium Series 1995; 210: London, Royal Society Medicine: 9–17.
3. Klein J. Otitis media. Clin Infect Dis 1994; **19**: 823–33.
4. Nguyen-Van-Tam J, Neal KR. Clinical effectiveness, policies, and practices for influenza and pneumococcal vaccines. Semin Resp Infect 1999; **14**: 184–95.
5. Lee C-J, Banks SD, Li JP. Virulence, immunity, and vaccine related to *Streptococcus pneumoniae*. Crit Rev Microbiol 1991; **18**: 89–114.
6. Sniadack DH, Schwartz B, Lipman H, et al. Potential interventions for the prevention of childhood pneumonia: geographic and temporal differences in serotype and serogroup distribution of sterile site pneumococcal isolates from children – implications for vaccine strategies. Pediatr Infect Dis J 1995; **14**: 503–10.
7. Klein DL. Pneumococcal disease and the role of conjugate vaccines. Microb Drug Resist 1999; **5**: 147–57.
8. Klein JO. The epidemiology of pneumococcal disease in infants and children. Rev Infect Dis 1981; **3**: 246–53.
9. Scott J, Hall A, Dagan R, Dixon J, et al. Serogroup-specific epidemiology of *Streptococcus pneumoniae*: associations with age, sex, and geography in 7000 episodes of invasive disease. Clin Infect Dis 1996; **22**: 973–81.
10. Ghaffar F, Friedland IR, McCracken GH. Dynamics of nasopharyngeal colonization by *Streptococcus pneumoniae*. Pediatr Infect Dis J 1999; **18**: 638–46.
11. Appelbaum P. Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. Clin Infect Dis 1992; **15**: 77–83.
12. Hausdorff WP, Bryant J, Kloek C, Paradiso PR, Siber GR. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, Part II. Clin Infect Dis 2000; **30**: 122–40.
13. Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, Part I. Clin Infect Dis 2000; **30**: 100–21.
14. Schrag S, Beall B, Dowell S. Limiting the spread of resistant pneumococci: biological and epdemiologic evidence for the effectiveness of alternative interventions. Clin Microbiol Rev 2000; **13**: 588–601.
15. Eskola J, Anttila M. Pneumococcal conjugate vaccines. Pediatr Infect Dis J 1999; **18**: 543–51.
16. Dagan R, Melamed R, Muallem M, Piglansky L, Yagupsky P. Nasopharyngeal colonization in southern Israel with antibiotic-resistant pneumococci during the first 2 years of life: relation to serotypes likely to be included in pneumococcal conjugate vaccines. J Infect Dis 1996; **174**: 1352–5.
17. Mbelle N, Huebner RE, Wasas AD, et al. Immunogenecity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis 1999; **180**: 1171–6.
18. Kyaw MH, Clarke S, Edwards G, Jones IG, Campbell H. Serotypes/groups distribution and antimicrobial resistance of invasive pneumococcal isolates: implication for vaccine strategies. Epidemiol Infect 2000; **125**: 561–72.
19. Smart LE. Serotyping of *Streptococcus pneumoniae* strains by coagglutination. J Clin Pathol 1986; **39**: 328–31.
20. Robbins JB, Austrian R, Lee C-J, et al. Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within serogroups. J Infect Dis 1983; **148**: 1136–59.
21. Yu X, Gray B, Chang Swei-ju, Ward JI, Edwards KM, Nahm MH. Immunity to cross-reactive serotypes induced by pneumococcal conjugate vaccines in infants. J Infect Dis 1999; **180**: 1569–76.

22. Smart L, Dougall A, Girdwood R. New 23-valent pneumococcal vaccine in relation to pneumococcal serotypes in systemic and non-systemic disease. J Infect 1987; **14**: 209–15.
23. Ridgway E, Tremlett C, Allen K. Capsular serotypes and antibiotic sensitivity of *Streptococcus pneumoniae* isolated from primary-school children. J Infect 1995; **30**: 245–51.
24. Colman G, Cooke E, Cookson B, Cooper P, Efstratiou A, George R. Pneumococci causing invasive disease in Britain 1982–1990. J Med Microbiol 1998; **47**: 17–27.
25. Jamal F. Epidemiological data on pneumococcal infections in Asian countries. Vaccine 1999; **17**: S75–8.
26. Butler J, Breiman R, Lipman H, Hofmann J, Facklam R. Serotypes distribution of *Streptococcus pneumoniae* infections among preschool children in the United States, 1978–1994: implications for development of a conjugate vaccine. J Infect Dis 1995; **171**: 885–9.
27. Hendley J, Sande M, Stewart P, Gwaltney MJ. Spread of *Streptococcus pneumoniae* in families. Carriage rates and distribution of types. J Infect Dis 1975; **132**: 55–61.
28. Gray B, Converse G, Dillion HJ. Epidemiologic studies of *Streptococcus pneumoniae* in infants: acquisition, carriage, and infection during the first 24 months of life. J Infect Dis 1980; **142**: 923–33.
29. Mastro T, Ghafoor A, Nomani N, et al. Antimicrobial resistance of pneumococci in children with acute lower respiratory tract infection in Pakistan. Lancet 1991; **337**: 156–9.
30. Craig AS, Erwin PC, Schaaffner W, et al. Carriage of multi-resistant *Streptococcus pneumoniae* and impact of chemoprophylaxis during an outbreak of meningitis at a day care center. Clin Infect Dis 1999; **29**: 1257–64.
31. Lehmann D, Gratten M, Montgomery J. Susceptibility of pneumococcal carriage isolates to penicillin provides a conservative estimate of susceptibility of invasive pneumococci. Pediatr Infect Dis J 1997; **16**: 297–305.
32. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenecity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000; **19**: 187–95.
33. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001; **344**: 403–9.
34. Murphy T, Henderson F, Clyde W, et al. Pneumonia: an eleven year study in a pediatric practice. Am J Epidemiol 1981; **113**: 12–21.
35. Heiskanen-Kosma T, Korppi M, Jokinen C, Kurki S. Etiology of childhood pneumonia: serologic results of a prospective, population based study. Pediatr Infect Dis J 1998; **17**: 986–91.
36. Djuretic T, Ryan M, Miller E, Fairley C, Goldblatt D. Hospital admissions in children due to pneumococcal pneumonia in England. J Infect Dis 1998; **37**: 54–8.
37. Teele D, Klein J, Rosner B, et al. Epidemiology of otitis media during the first seven years of life in children in Greater Boston: a prospective, cohort study. J Infect Dis 1989; **160**: 83–94.
38. Montgomery J, Lehmann D, Smith T, et al. Bacterial colonization of the upper respiratory tract and its association with acute respiratory tract infections in Highland children of Papua New Guinea. Rev Infect Dis 1990; **12** (Suppl 8): S1006–16.
39. Black S. The Kaiser Permanente Efficacy Trial: update otitis media (presentation). Second International Symposium of Pneumococci and Pneumococcal Diseases, 2000. Presentation available at ⟨http://216.247.185.154/isppd00/is0b0810/maib0810.htm⟩. Accessed 21 December 2000.
40. Kelly T, Dillaard J, Yother J. Effect of genetic switching of capsular type on virulence of *Streptococcus pneumoniae*. Infect Immun 1994; **62**: 1813–9.
41. Nesin M, Ramirez M, Tomasz A. Capsular transformation of a multidrug-resistant *Streptococcus pneumoniae* in vivo. J Infect Dis 1998; **177**: 707–13.
42. Lipsitch M. Bacterial vaccines and serotypes replacement: lessons from *Haemophilus influenzae* and prospects for *Streptococcus pneumoniae*. Emerg Infect Dis 1999; **5**: 336–45.
43. Spratt BG, Greenwood BM. Prevention of pneumococcal disease by vaccination: does serotype replacement matter? Lancet 2000; **365**: 1210–11.

Scand J Infect Dis 34: 289–298, 2002

Taylor&Francis healthsciences

The Changing Epidemiology of Bacterial Meningitis and Invasive Non-meningitic Bacterial Disease in Scotland During the Period 1983–99

MOE H. KYAW[1,2], PETER CHRISTIE[2], IAN G. JONES[2] and HARRY CAMPBELL[1]

From the [1]Public Health Sciences, University of Edinburgh, Edinburgh, UK and [2]Scottish Centre for Infection and Environmental Health, Glasgow, UK

We reviewed population-based laboratory reports of invasive meningococcal, pneumococcal, Haemophilus influenzae, Group B Streptococcus (GBS) and Listeria monocytogenes isolates in order to examine the changing epidemiology of meningitis and invasive non-meningitic disease (INMD) caused by these 5 pathogens in the 2 periods before (1983–91) and after (1992–99) routine use of H. influenzae type B conjugate vaccine (Hib) in Scotland. Neissieria meningitidis was the most common cause of meningitis, accounting for 39.2% of cases of meningitis in 1983–91 and 47% of cases in 1992–99, followed by H. influenzae (31%), Streptococcus pneumoniae (22.4%), GBS (3.9%) and L. monocytogenes (3.5%) in 1983–91 and S. pneumoniae (36.3%), H. influenzae (7.8%), GBS (6.1%) and L. monocytogenes (2.8%) in 1992–99. The important epidemiological features of meningitis and INMD caused by these 5 pathogens between 1983–91 and 1992–99 include:

1. **The incidence of bacterial meningitis due to S. pneumoniae and GBS was stable;**
2. **S. pneumoniae was the predominant cause of INMD in both periods;**
3. **The incidences of INMD caused by N. meningitidis, GBS and S. pneumoniae increased, by 27%, 55% and 56%, respectively;**
4. **Decreases in the incidences of bacterial meningitis (by 50%) and INMD (by 50%) due to L. monocytogenes were detected; and**
5. **There were dramatic reductions in the proportions of bacterial meningitis (by 92%) and INMD (by 56%) due to H. influenzae in vaccinated and non-vaccinated individuals.**

Continued surveillance is necessary to monitor the disease trend, population at risk, serotype distribution and antimicrobial susceptibility in order to implement appropriate public health interventions against invasive bacterial disease.

M. H. Kyaw, Scottish Centre for Infection and Environmental Health, Clifton House, Clifton Place, Glasgow G3 7LN, UK. Tel: +44 141 300 1184; Fax: +44 141 300 1170; E-mail: Moe.Kyaw@scieh.csa.scot.nhs.uk

INTRODUCTION

Bacterial meningitis and invasive non-meningitic bacterial disease (INMD) are important causes of morbidity and mortality worldwide (1–6). Before the implementation of universal Haemophilus influenzae type B (Hib) conjugate vaccination in the US and Europe, Hib accounted for 50–75% of cases of meningitis or other bacterial invasive disease in children aged <5 y (2, 7, 8). The use of Hib conjugate vaccines has dramatically reduced the incidence of invasive Hib disease and has altered the epidemiology of invasive bacterial disease. Surveillance data from the US have shown that Streptococcus pneumoniae is now the most common cause of bacterial meningitis or other bacterial invasive disease, followed by Neissieria meningiditis, Group B Streptococcus (GBS), Listeria monocytogenes and H. influenzae (3). No similar review of invasive bacterial disease has been carried out in the UK since the introduction of Hib vaccination in October 1992. Polysaccharide or conjugate vaccines are available to protect against some serotypes/groups of H. influenzae, S. pneumoniae and N. meningitidis. Therefore, a review of the epidemiology of invasive bacterial disease is important in order to make rational decisions concerning future prevention and control strategies for bacterial meningitis and INMD in Scotland.

The aim of this study was to define the epidemiological features of invasive bacterial disease between 1983 and 1999 and to examine the changing pattern of meningitis and INMD between 1983–91 and 1992–99 using the available population-based laboratory data.

MATERIALS AND METHODS

The study data were obtained from the Scottish Centre for Infection and Environmental Health (SCIEH), which serves as a national surveillance centre for infectious diseases and environmental health hazards in Scotland. Laboratory records of cases of S. pneumoniae, N. meningitidis, H. influenzae, GBS and L. monocytogenes reported to the SCIEH during the period 1983–99 were reviewed. We only included invasive isolates from blood, cerebrospinal fluid (CSF) and other sterile fluids (pleural fluid, ascitic fluid, synovial fluid and tissue aspirates) in the study. Duplicate isolates were excluded. Bacterial meningitis was defined by the isolation of bacteria from CSF or blood and CSF. Isolates from blood or other normally sterile sites but not from CSF were regarded as INMD, although some of these may have been diagnosed clinically as meningitis. Information on demographic characteristics (age, sex and geographic location) and the time when the isolate was obtained were available from laboratory reports.

We determined the annual proportions of meningitis and INMD due to the 5 pathogens between 1983 and 1999. Two time periods (1983–91 and 1992–99) were chosen in order to examine the changing patterns of meningitis and INMD in different age groups before and after the routine use of Hib vaccine, which was intro-

 DOI: 10.1080/00365540110080403

duced in October 1992. The 2 midpoint years (1987 and 1996) were used to calculate the age-specific incidence rates for the 2 periods. The number of laboratories reporting to the SCIEH has increased during these 2 periods: from 29 to 33 for S. pneumoniae and N. meningitidis, from 25 to 28 for GBS and H. influenzae and from 15 to 22 for L. monocytogenes. A consultant physician was responsible for reviewing these laboratory data every week to ensure completeness and reliability. Although all existing laboratories have reported cases caused by these pathogens to the SCIEH during the study period, the laboratory collection system relies on the voluntary reporting of cases by these laboratories. Therefore, invasive disease is likely to be under-reported, particularly as identified from blood cultures. During the study period, the methods of diagnosis for these pathogens (such as non-cultural diagnosis using molecular methods) and the clinical practice of clinicians taking blood/CSF cultures for these pathogens have also changed substantially and may affect the results. Nevertheless, our large population-based passive surveillance system provides data on the relative importance of the 5 pathogens during the 2 time periods. Information on antibiotic prescribing for the whole of Scotland was obtained from the Information and Statistics Division (ISD) of the Common Services Agency of the National Health Services (NHS), Scotland.

Data analysis

Statistical analysis was performed using SPSS version 10. The χ^2 test was used to compare variables. $p < 0.05$ was considered statistically significant.

RESULTS

A total of 12,108 invasive isolates were identified during the study period, of which 2514 (20.8%) were obtained from CSF. The annual relative contributions of meningitis and INMD due to N. meningitidis, S. pneumoniae, H. influenzae, GBS and L. moncytogenes between 1983 and 1999 are presented in Figs 1 and 2, respectively. The proportions and incidences of meningitis and INMD caused by these 5 pathogens between 1983–91 and 1992–99 are shown in Table I. Age-specific incidence rates for meningitis and INMD varied with the pathogen (Tables II and III). Cases of meningitis ($n = 1317$ vs. 1151) and INMD ($n = 4822$ vs. 4512) were more numerous in males than in females. All 5 pathogens showed some seasonal variations (Figs 3 and 4). The overall changes in the incidences of bacterial meningitis and INMD caused by these 5 pathogens were a 50% decrease (from 3.8 to 1.9 per 100,000 population) and a 30% increase (from 9.7 to 12.6 per 100,000 population), respectively between 1983–91 and 1992–99 (Table I). The prescription of all antimicrobial agents in Scotland also increased between the 2 periods (data not shown).

N. meningitidis

N. meningitidis was the most common cause of meningitis and the third most common cause of INMD in 1983–91 and in 1992–99. The overall changes in the incidences of meningitis and INMD due to N. meningitidis were a 40% decrease (from 1.5 to 0.9 per 100,000 population) and a 27% increase (from 1.1 to 1.4 per 100,000 population), respectively between these 2 periods (Table I). An increase

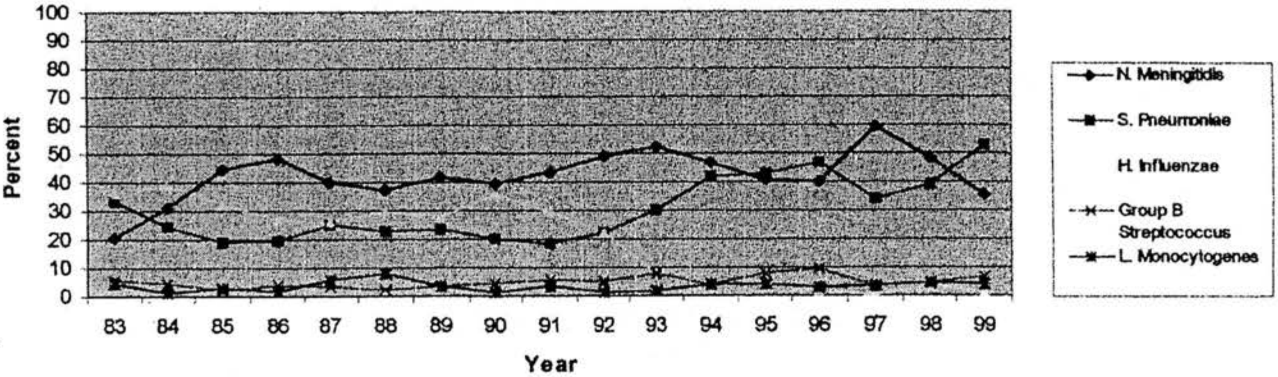


Fig. 1. Proportion of bacterial meningitis caused by the 5 pathogens during the period 1983–99.

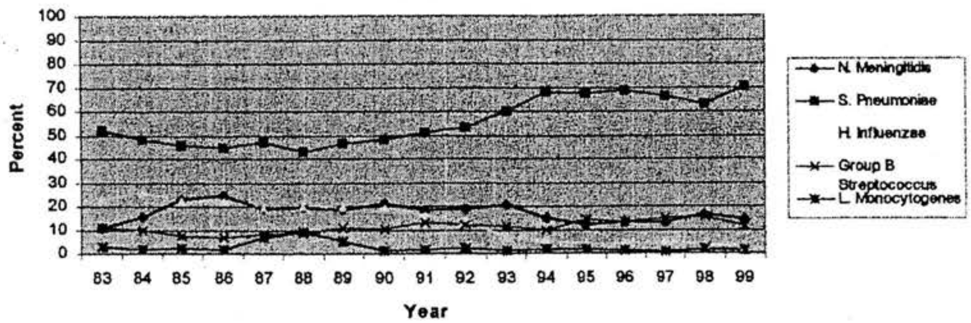


Fig. 2. Proportion of INMD caused by the 5 pathogens during the period 1983–99.

Table I. *Frequency and incidence of bacterial meningitis and INMD by pathogen between 1983–91 and 1992–99*

	1983-91			1992-99			
Causative pathogen	No. of cases	%	Mean annual incidence (per 100,000 population)	No. of cases	%	Mean annual incidence (per 100,000 population)	Percent change in disease incidence between 1983-91 and 1992-99
Bacterial meningitis							
N. meningitidis	681	39.2	1.5	365	47	0.9	−40
S. pneumoniae	389	22.4	0.8	282	36.3	0.7	−12.5
H. influenzae	539	31	1.2	61	7.8	0.1	−91.7
GBS	68	3.9	0.1	47	6.1	0.1	0
L. monocytogenes	60	3.5	0.1	22	2.8	0.05	−50
Total	1,737	100	3.8	777	100	1.9	−50
Non-meningitic disease							
N. meningitidis	507	11.4	1.1	555	10.8	1.4	+27.3
S. pneumoniae	2,518	56.7	5.5	3,540	68.7	8.6	+56.4
H. influenzae	732	16.5	1.6	280	5.4	0.7	−56.3
GBS	520	11.7	1.1	711	13.8	1.7	+54.5
L. monocytogenes	167	3.7	0.4	64	1.3	0.2	−50
Total	4,444	100	9.7	5,150	100	12.6	+29.9

in the proportion of cases of invasive meningococcal disease was observed in all age groups except for the 15–44 y age group for meningitis and the >45 y age group for INMD (Tables II and III). Most cases of meningococcal meningitis (61%) and invasive non-meningitic meningococcal disease (54%) occurred in the ≤ 4 y age group ($p < 0.0001$ each). The proportions of meningitis and INMD due to N. meningitidis were higher in the ≤ 24 y age group. A seasonal pattern of meningococcal meningitis and invasive non-meningitic meningococcal disease activity was observed, with peaks during the first and last 4 weeks of the year (Figs 3 and 4). Of the 1046 CSF isolates, serogroup information was available for only 150 (20%), with the predominant serogroups being B (52%) and C (46%).

S. pneumoniae

S. pneumoniae was the most common cause of INMD and the second most common cause of meningitis between 1983–91 and 1992–99. During these 2 periods, the incidence of meningitis caused by S. pneumoniae decreased by 12.5% (from 0.8 to 0.7 per 100.000 population) and that of INMD increased by 56% (from 5.5 to 8.6 per 100,000 population) (Table I). An increase in invasive disease due to S. pneumoniae was noted in all age groups except for the 5–14 y and 45–64 y age groups for meningitis and the 5–24 y age group for INMD (Table II and Table III). Those aged <5 y showed the greatest increases in the proportions of cases of meningitis and INMD due to S. pneumoniae between the periods 1983–91 and 1992–99. Cases of pneumococcal meningitis were more numerous in the age groups <1 y ($p < 0.0001$) and ≥ 45 y ($p < 0.0001$) compared with other age groups during the period 1983–99. The risk of invasive non-meningitic pneumococcal disease was highest in the elderly, accounting for 49.2% of cases of other invasive pneumococcal disease in 1983–99. A seasonal trend of pneumococcal meningitis and invasive non-meningitic pneumococcal disease activity was noted (Figs 3 and 4). The peak number of cases occurred in the first and last 4 weeks of the year for INMD. The seasonal pattern of pneumococcal meningitis was less distinctive. Data on serogroups were recorded for 5.3% (320/6058) of invasive non-meningitic pneumococcal isolates and for 8.5% (57/671) of pneumococcal meningitis isolates. Of these, 11-valent pneumococcal conjugate vaccine serotypes/groups 14, 3, 4, 1, 9, 6, 19, 18, 7, 23 and 5 (in descending order) accounted for 80.6% (304/377) of all serotyped/grouped invasive isolates. The 7- and 9-valent pneumococcal conjugate vaccine serotypes/groups caused 54.6% (206/304) and 63.7% (240/304) of all cases of invasive disease, respectively.

H. influenzae

H. influenzae was the second most common cause of bacterial meningitis and INMD in 1983–91, accounting for 539 (31%) and 732 (17%) cases, respectively (Table I). As a result of the routine Hib vaccination programme, the overall reductions in the incidences of meningitis and INMD due to H. influenzae were 92% (from 1.2 to 0.1 per 100,000 population) and 56% (from 1.6 to 0.7 per 100,000 population), respectively for all age groups between 1983–91 and 1992–99 (Table I). During the second study period, H. influenzae was the third most common cause of meningitis and the fourth most common cause of INMD. The relative proportions of meningitis and INMD due to H. influenzae

Table II. *Proportion of bacterial meningitis caused by the 5 pathogens during the periods 1983–91 and 1992–99 by age group*

		N. meningitidis			S. pneumoniae			H. influenzae			GBS			L. monocytogenes		
Age group (y)	Period	Cases	%	Incidence[a]	Cases	%	Incidence[a]	Cases	%	Incidence[a]	Cases	%	Incidence[a]	Cases	%	Incidence[a]
<1	1983–91	184	36.1	31.2	71	13.9	12	184	36.1	31.2	53	10.4	9	17	3.3	2.9
	1992–99	109	48.9	23.2	58	26	12.4	15	6.7	3.2	37	16.6	7.9	4	1.7	0.9
1–4	1983–91	218	38.8	9.4	44	7.8	1.9	293	52.2	12.7	0	0	0	6	1.1	0.3
	1992–99	108	57.1	5.3	46	24.3	2.3	34	18	1.7	0	0	0	1	0.5	0.05
5–14	1983–91	81	58.7	1.4	37	26.8	0.6	20	14.5	0.3	0	0	0	0	0	0
	1992–99	38	73.1	0.7	11	21.2	0.2	2	3.8	0.04	0	0	0	1	1.9	0.02
15–24	1983–91	103	82.4	1.3	18	14.4	0.2	3	2.4	0.04	1	0.8	0.01	0	0	0
	1992–99	52	76.5	1	15	22.1	0.3	1	1.5	0.02	0	0	0	0	0	0
25–44	1983–91	28	32.9	0.2	42	49.1	0.3	8	9.4	0.06	4	4.7	0.03	3	3.5	0.02
	1992–99	21	29.2	0.2	42	58.3	0.3	3	4.2	0.02	4	5.6	0.03	2	2.8	0.02
45–64	1983–91	32	22.5	0.3	90	63.4	0.9	5	3.5	0.05	3	2.1	0.03	12	8.5	0.1
	1992–99	24	31.2	0.3	43	55.8	0.5	3	3.9	0.03	2	2.6	0.02	5	6.5	0.05
≥65	1983–91	9	9	0.1	67	67	1	4	4	0.06	3	3	0.04	17	17	0.3
	1992–99	9	11	0.1	64	78	1	0	0	0	0	0	0	9	11	0.1
N/A	1983–91	26	30.2	0.1	29	33.7	0.1	22	25.6	0.05	4	4.7	0	5	5.8	0
	1992–99	4	28.6	0	3	21.4	0	3	21.4	0	4	28.6	0	0	0	0
All ages	1983–91	681	39.2	1.5	389	22.4	0.8	539	31	1.2	68	3.9	0.1	60	3.5	0.1
	1992–99	365	47	0.9	282	36.3	0.7	61	7.8	0.1	47	6.1	0.1	22	2.8	0.05

[a] Rate per 100,000 population.
N/A = age information not available.

Table III. *Proportion of INMD caused by the 5 pathogens during the periods 1983–91 and 1992–99 by age group*

Age group (y)	Period	N. meningitidis			S. pneumoniae			H. influenzae			GBS			L. monocytogenes		
		Cases	%	Incidence[a]	Cases	%	Incidence[a]	Cases	%	Incidence[a]	Cases	%	Incidence[a]	Cases	%	Incidence[a]
<1	1983–91	109	17.7	18.5	119	19.3	20.2	161	26.1	27.3	192	31.2	32.6	35	5.7	5.9
	1992–99	100	21.1	21.3	114	24.1	24.3	31	6.6	6.6	223	47.1	47.5	5	1.1	1.1
1–4	1983–91	175	22.7	7.6	219	28.5	9.5	369	47.9	16	5	0.6	0.2	2	0.3	0.1
	1992–99	161	40.8	7.9	174	44.2	8.5	57	14.5	2.8	2	0.5	0.1	0	0	0
5–14	1983–91	61	32.8	1.1	89	47.8	1.5	34	18.3	0.6	2	1.1	0.03	0	0	0
	1992–99	82	50.3	1.6	61	37.4	1.2	14	8.6	0.3	5	3.1	0.1	1	0.6	0.02
15–24	1983–91	69	29.9	0.9	102	44.2	1.3	14	6.1	0.2	29	12.5	0.4	17	7.3	0.2
	1992–99	97	42.5	1.9	94	41.2	1.8	7	3.1	0.1	28	12.3	0.5	2	0.9	0.04
25–44	1983–91	14	3.5	0.1	240	60	1.9	32	8	0.2	78	19.5	6.1	36	9	0.3
	1992–99	36	6.1	0.3	419	70.4	3.4	23	3.9	0.2	111	18.6	0.9	6	1	0.05
45–64	1983–91	27	4.1	0.3	528	79.4	5.3	34	5.1	0.3	59	8.9	0.6	17	2.5	0.2
	1992–99	28	3	0.3	740	79.8	7.8	45	4.9	0.5	99	10.7	1	15	1.6	0.2
≥65	1983–91	24	1.9	0.4	1,058	83.6	15.7	48	3.8	0.7	103	8.1	1.5	33	2.6	0.5
	1992–99	35	1.7	0.6	1,753	82.8	28	95	4.5	1.5	200	9.4	3.2	34	1.6	0.5
N/A	1983–91	28	9.0	0.1	163	52.6	0.4	40	12.9	0.1	52	16.8	0.1	27	8.7	0.06
	1992–99	16	6.3	0.04	185	73.1	0.4	8	3.2	0.02	43	17.0	0.1	1	0.4	0
All ages	1983–91	507	11.4	1.1	2,518	56.7	5.5	732	16.5	1.6	520	11.7	1.1	167	3.7	0.4
	1992–99	555	10.8	1.4	3,540	68.7	8.6	280	5.4	0.7	711	13.8	1.7	64	1.3	0.2

[a] Rate per 100,000 population.
N/A = age information not available.

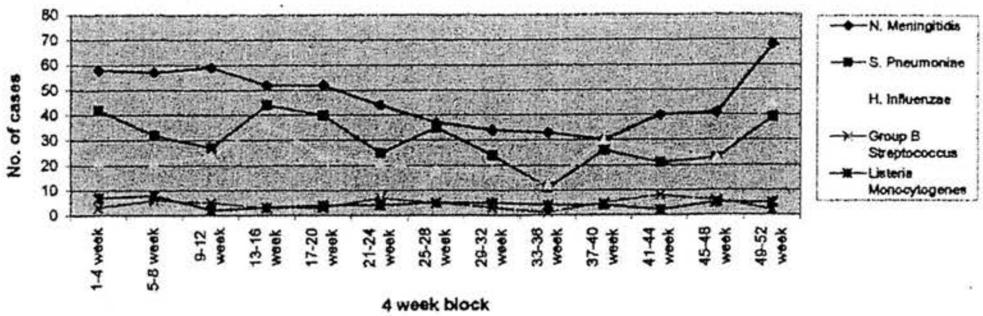


Fig. 3. Seasonal pattern of meningitis caused by the 5 pathogens over 4-week blocks of the year during the period 1983–99.

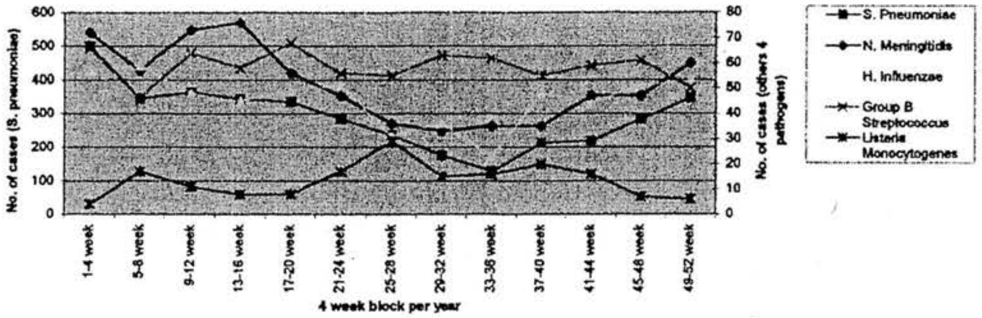


Fig. 4. Seasonal pattern of INMD caused by the 5 pathogens over 4-week blocks of the year during the period 1983–99.

decreased in all age groups except for the 45–64 y age group for meningitis and the ≥ 65 y age group for INMD (Tables II and III). A marked reduction in cases of meningitis and INMD due to H. influenzae was seen in children and adults who had not received Hib vaccine as well as in the vaccinated group aged < 4 y. A biphasic seasonal pattern of H. influenzae meningitis and invasive non-meningitic H. influenzae was observed (Figs 3 and 4). Serotype information was available for 787 (48.8%) cases of invasive disease between 1983 and 99: serotype B was responsible for 99.7% (367/368) of cases of meningitis and 99.5% (417/419) of cases of INMD.

GBS

Between 1983–91 and 1992–99, the overall incidence of GBS meningitis remained the same but there was a 55% increase (from 1.1 to 1.7 per 100,000 population) in the incidence of INMD caused by GBS (Table I). Marked increases in the proportions of cases of meningitis ($p < 0.0001$) and INMD ($p < 0.0001$) caused by GBS were seen in the < 1 y age group compared to other age groups between these 2 periods (Table II and Table III). Children aged < 1 y had the highest risks of GBS meningitis and non-meningitic disease, accounting for 84.1% and 36.5% of all cases, respectively in 1983–99. The second highest proportion of cases of bacterial meningitis and INMD due to GBS occurred in the 15–44 y age group. Seasonal variations in GBS meningitis and INMD disease activity were recorded throughout the study period (Figs 3 and 4).

L. monocytogenes

Overall reductions in the incidences of meningitis (50%; from 0.1 to 0.05 per 100,000 population) and INMD (50%; from 0.4 to 0.2 per 100,000 population) due to L. monocytogenes were documented between 1983–91 and 1992–99 (Table I). A decline in the number of cases of meningitis and INMD caused by L. monocytogenes was noted in all age groups except for the 5–14 y age group for meningitis and the 5–14 y and ≥ 65 y age groups for INMD (Tables II and III). A marked decline in the number of cases of Listeria meningitis (from 17 to 4) and invasive non-meningitic listerial disease (from 35 to 5) in children aged < 1 y was noted between 1983–91 and 1992–99. The greatest increase in the proportion of cases of bacterial meningitis and INMD caused by L. monocytogenes was noted in the ≥ 65 y age group. A seasonal variation in listerial meningitis and invasive non-meningitic listerial disease activity was recorded (Figs 3 and 4). Serotyping was performed for 17/82 (20.7%) of the CSF isolates and for 33/73 (45.2%) of other invasive isolates. Serotypes 4, 4b, 1 and 1/2 caused all serotyped cases of listerial meningitis and invasive non-meningitic listerial disease.

DISCUSSION

Despite the availability of antibiotics and the advances made in producing effective vaccines for S. pneumoniae, H. influenzae type B and N. meningitidis, bacterial meningitis continues to have a case fatality rate of 5–40%, with 9–30% of cases who survive showing neurological deficits (3, 9, 10). Studies in the US have also shown a 56.4% reduction in the incidence of bacterial meningitis and a 43.7% increase in the incidence of invasive bacterial disease caused by these 5 pathogens in 1995 compared with 1986 (3, 7). The increased number of blood cultures obtained from patients with febrile illness could be responsible for the increase in the number of cases of INMD.

In this study, conducted between 1983–91 and 1992–99, the most important findings were:

1. The incidence of bacterial meningitis due to S. pneumoniae and GBS was stable;
2. S. pneumoniae was the predominant cause of INMD in both periods;
3. The incidences of INMD caused by N. meningitidis, GBS and S. pneumoniae increased, by 27%, 55% and 56%, respectively;
4. Decreases in the incidences of bacterial meningitis (by 50%) and INMD (by 50%) due to L. monocytogenes were detected; and
5. There were dramatic reductions in the proportions of bacterial meningitis (by 92%) and INMD (by 56%) due to H. influenzae in vaccinated and non-vaccinated individuals.

Changes in age-specific disease trends as a result of vaccination against Hib were identified as in previous reports from the US and UK (3, 11). This has important implications for current age-based preventive and treatment guidelines.

N. meningitidis was the commonest cause of bacterial meningitis in the present study. The US studies reported that N. meningitidis was the leading cause of bacterial meningitis in the ≤ 5 y (12) and 2–18 y (3) age groups. Our results indicated that N. meningitidis was the predominant cause of meningitis in the age group 5–24 y. In common with other reports (2, 3, 13), we found that the risks of meningococcal meningitis and invasive non-meningitic meningococcal disease were highest in infants and young children aged 1–4 y. Implementation of serogroup C meningococcal conjugate vaccine into the UK primary immunization schedule has been reported to reduce the incidence of serogroup C disease by 92–97% in vaccinated groups (14). This may also have a substantial impact on the current distribution of meningoccal serogroups as well as a shift in the distribution of disease in the > 18 y age group that is not currently targeted for vaccination. In the present study, at least 52% of cases of meningococcal disease were due to serogroup B. This highlights the importance of developing an effective vaccine against serogroup B in order to further reduce the burden of bacterial meningitis.

S. pneumoniae was the second most frequent cause of meningitis in Scotland. Data from other developed countries showed that S. pneumoniae was the predominant cause of bacterial meningitis and invasive disease in the US (3) and the second most frequent cause of bacterial meningitis in Italy (15). In the US, 20–26% of cases of invasive pneumococcal disease occurred in children aged < 5 y (3, 16). In the present study, 32.6% of cases of pneumococcal meningitis and 10.3% of cases of other invasive pneumococcal disease occurred in children aged < 5 y. Our previous report (17) showed that the prevalence of penicillin and erythromycin non-susceptible pneumococci has increased, from 4.2% in 1992 to 12.6% in 1999 and from 5.6% in 1994 to 16.3% in 1999, respectively. As a 7-valent pneumococcal conjugate vaccine has been shown to prevent 97.4% of cases of invasive disease and to reduce nasopharyngeal carriage of vaccine serotypes in infants and young children, which is particularly associated with drug resistance (18, 19), the future routine use of conjugate vaccine in the UK could have a substantial impact on the incidence of invasive pneumococcal disease and on drug resistance in this age group. Consistent with other reports (20), the proportion of INMD caused by S. pneumoniae was higher in the age groups ≥ 45 y and ≥ 65 y. As the serotypes/serogroups in the 23-valent polysaccharide vaccine covered $> 90\%$ of the older age groups in Scotland (21), greater use of this vaccine might reduce the burden of invasive pneumcoccal disease in the elderly. However, coverage of pneumococcal polysaccharide vaccine was low among recommended patients: 4–15% in the UK (22, 23). We found that $< 65\%$ of disease-causing serotypes were covered by the 7- and 9-valent conjugate vaccines in all age groups, indicating a need for a conjugate vaccine with > 9 serotypes for the older age groups. As yet, the efficacy of conjugate vaccines has not defined in adults and other high-risk groups and requires further research.

The dramatic decline in invasive H. influenzae disease after routine Hib vaccination documented in the present study was similar to that reported in other UK studies (2, 11). Our findings also showed similar reductions in the proportions of cases of meningitis and INMD due to H. influenzae. Data from this study and the previous report (24) clearly indicate that important progress has been achieved in reducing Hib invasive disease in children aged < 5 y in a country with universal Hib vaccination. Hib vaccine coverage was $> 95\%$ in target groups in Scotland and has been reported to have 97% effectiveness in children aged 5–71 months (with an estimated vaccine failure rate of 2.2 per 100,000 in vaccine recipients) (25). Our study also showed marked reductions in H. influenzae meningitis and INMD in those who were not targeted for Hib vaccination, indicating a clear herd immunity effect as observed in other studies in the US (26, 27) and UK (28). Although we did not find a notable increase in the occurrence of invasive H. influenzae disease among children aged > 5 y, such findings have recently been reported in the US (28, 29). Our study confirmed that serotype B remains the dominant cause of invasive H. influenzae disease. Complete ascertainment of serotype information is necessary in order to monitor the effectiveness of the vaccination programme and any possible future increase in non-type B H. influenzae disease despite universal Hib immunization of infants in the future.

GBS is the most common cause of meningitis and INMD in neonates (3, 7, 30), with a case fatality rate of 4–6% (31, 32). The current study showed that the majority of cases of GBS meningitis and INMD occurred in children aged < 1 y. The major route of GBS transmission in infants is from their mothers, who are colonized with GBS in the genital tract (33). Chemoprophylaxis of pregnant women with risk factors for GBS is effective in reducing the incidence of GBS disease in infants (34). The increased use of prophylactic intrapartum antibiotics has been suggested to have reduced early-onset neonatal GBS disease by 65% over the period 1993–98 in the US (35). In agreement with Canadian (36) and US (37–39) studies, the present study found a higher proportion of cases of INMD due to GBS in adults during the period 1983–99. This may in part reflect the increased practice of blood culture collection for suspected cases and an increase in the prevalence of individuals with diabetes, cirrhosis, renal failure, stroke and breast cancer, all of whom are at increased risk of GBS disease (40). These data highlight the need for continued surveillance for GBS disease and for strategies to provide antimicrobial agents for selected women in Scotland. The development of conjugate GBS vaccines is now underway and could reduce the burden of disease and the need for antimicrobial agents as prophylactics in the future (41, 42).

Pregnant women, neonates, the elderly and the immunocompromised are at increased risk of invasive listerial infection (43). The majority of cases of listerial meningitis and invasive non-meningitic listerial disease occurred in children aged < 1 y and in adults aged ≥ 65 y in the present study. In common with US surveillance data (3, 7), we found that L. moncytogenes caused 11–17% of cases of bacterial meningitis in the ≥ 65 y age group and was the second most common cause of bacterial meningitis, after Pneumococcus. Evidence suggests that most listerial infections are caused by contaminated food (44). The 44% reduction in cases of invasive L. monocytogenes in the US (45) and the proportional decline in meningitis (12.2%; from 3.3% to 2.9%) and INMD (62.9%; from 3.5% to 1.3%) caused by L. monocytogenes in this report may be due to tight regulations on contaminated foods and dietary recommendations for high-risk individuals issued by the UK Departments of Health and the Centers for Disease Control in the US (46, 47), indicating that these preventive measures are effective. In line with previous published data (48), serotypes 4, 4b, 1 and 1/2 were responsible for almost all cases of meningitis and INMD. Therefore, they should be considered as the main candidate antigens for the development of any vaccine against this pathogen.

Certain limitations exist in our surveillance data. As only CSF isolates were regarded as meningitis, cases without CSF cultures which were blood culture-positive but with a clinical diagnosis of meningitis were classified as INMD. As a result of culture-negative cases and under-reporting, our data may underestimate the true incidence rate of disease caused by these 5 pathogens. The increased use of non-culture diagnostic methods and an increase in the number of reporting laboratories are also likely to have influenced the study results. However, the increase in the number of reporting laboratories for the major pathogens, namely Pneumococci, Meningococci, GBS and H. influenzae, was relatively small. Although an additional 7 laboratories reported L. monocytogenes, the number of cases due to this pathogen was small. In addition, cases of L. moncytogenes decreased over the study period. These data suggest that the increase in the number of laboratories reporting to the SCIEH during the study period is not likely to represent a primary explanation for the reported findings. Furthermore, pathogens that were not included in the study can cause meningitis and INMD. However, based on previous reports (49–51) meningitis and INMD due to other bacterial pathogens are much less common and should not have a major impact on the burden of disease.

CONCLUSIONS

Routine vaccination against H. influenzae type B and judicious use of antimicrobial agents has changed the epidemiological characteristics of bacterial meningitis and INMD in Scotland as assessed by routine surveillance data. The current widespread use of meningococcal Group C conjugate vaccine, the implementation of S. pneumoniae conjugate vaccines into the routine childhood immunization schedule and the successful development of meningococcal Group B or multivalent bacterial conjugate vaccines in the future could lead to major progress in the prevention and control of bacterial meningitis and INMD. In order to inform appropriate immunization policies and clinical practice, continuous surveillance of invasive bacterial disease is necessary to enable assessment of the changing pattern of disease incidence and determination of the populations at risk of disease, serotype distributions and antimicrobial susceptibilities.

ACKNOWLEDGEMENT

We thank the staff at the microbiology laboratories and at the SCIEH for carrying out data entry of the laboratory reports.

REFERENCES

1. Wenger J, Broome C. Bacterial meningitis: epidemiology. In: Lambert H, ed. Handbook of infectious diseases: infections of the central nervous system. Philadelphia, PA: B. C. Decker Inc, 1991: 16–31.
2. Urwin G, Yuan MF, Feldman RA. Prospective study of bacterial meningitis in North East Thames region, 1991-3, during introduction of Haemophilus influenzae vaccine. Br Med J 1994; 309: 1412–4.
3. Schuchat A, Robinson K, Wenger JD, Harrison LH, Farley M, Reingold AL, et al. Bacterial meningitis in the United States in 1995. N Engl J Med 1997; 337: 970–6.
4. Peltola H. Need for Haemophilus influenzae type b vaccination in Asia as evidenced by epidemiology of bacterial meningitis. Pediatr Infect Dis 1998; 17: S148–51.
5. Gold R. Epidemiology of bacterial meningitis. Infect Dis Clin N Am 1999; 13: 515–25.
6. Campagne G, Schuchat A, Djibo S, Ousseini A, Cisse L, Chippaux J. Epidemiology of bacterial meningitis in Niamey, Niger, 1981-1996. Bull World Health Organ 2000; 77: 499–508.

7. Wenger J, Hightower A, Facklam R, Gaventa S, Broome CV. Bacterial meningitis study group. Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. J Infect Dis 1990, 162: 1316–23.
8. Berg S, Trollfors B, Claesson BA, Alestig K, Gothefors L, Hugosson S, et al. Incidence and prognosis of meningitis due to Haemophilus influenzae, Streptococcus pneumoniae and Nessieria meningitidis in Sweden. Scand J Infect Dis 1996; 28: 247–52.
9. Baraff L, Lee S, Schriger D. Outcomes of bacterial meningitis in children: a meta-analysis. Pediatr Infect Dis J 1993; 12: 389–94.
10. Grimwood K, Anderson P, Anderson V, Tan L, Nolan T. Twelve year outcomes following bacterial meningitis: further evidence for persisting effects. Arch Dis Child 2000; 83: 111–6.
11. Hargreaves RM, Slack MPE, Howard AJ, Anderson E, Ramsay ME. Changing patterns of invasive Haemophilus influenzae disease in England and Wales after introduction of the Hib vaccination programme. Br Med J 1996; 312: 160–1.
12. Loughlin AM, Marchant CD, Lett SM. The changing epidemiology of invasive bacterial infections in Massachusetts children. Am J Publ Health 1995; 85: 392–4.
13. Rosenstein NE, Perkins BA, Stephens DS, Lefkowitz L, Carttcr ML, Danila R, et al. The changing epidemiology of meningococcal disease in the United States, 1992-1996. J Infect Dis 1999; 180: 1894–901.
14. Ramsay ME, Andrews N, Kaczmarski EB, Miller E. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. Lancet 2001; 357: 195–6.
15. Salmaso S, Mastrantonio P, Scuderi G. Pattern of bacterial meningitis in Italy. Eur J Epidemiol 1997; 13: 317–21.
16. Robinson KA, Baughman W, Rothrock G, Barrett NL, Pass M, Lexau C, et al. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998. Opportunities for prevention in the conjugate vaccine era. JAMA 2001; 285: 1729–35.
17. Kyaw MH, Clarke S, Jones IG, Campbell H. Incidence of invasive pneumococcal disease in Scotland, 1988-1999, Epidemiol Infect 2002.
18. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, et al. Efficacy, safety and immunogenecity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000; 19: 187–95.
19. Dagan R, Fraser D. Conjugate pneumococcal vaccine and antibiotic resistant Streptococcus pneumoniae and reduction of otitis morbidity. Pediatr Infect Dis J 2000; 19 (Suppl): S79–88.
20. Butler JC, Schuchat A. Epidemiology of pneumococcal infections in the elderly. Drugs Aging 1999; 15: 11–9.
21. Kyaw MH, Clarke S, Edwards G, Jones IG, Campbell H. Serotypes/groups distribution and antimicrobial resistance of invasive pneumococcal isolates: implication for vaccine strategies. Epidemiol Infect 2000; 125: 561–72.
22. McDonald P, Friedman E, Banks A, Anderson R, Carman V. Pneumococcal vaccine campaign based in general practices. Br Med J 1997; 314: 1094–8.
23. Kyaw MH, Nguyen-Van-Tam J, Pearson J. Family doctor advice is the main determinant of pneumococcal vaccine uptake. J Epidemiol Commun Health 1999; 53: 589–90.
24. Centers for Disease Control and Prevention. Progress toward eliminating Haemophilus influenzae type b disease among infants and children—United States, 1987-1997. MMWR Morb Mortal Wkly Rep 1998; 47: 993–8.
25. Heath PT, Booy R, Azzopardi HJ, Slack MP, Bowen-Morris J, Griffiths H, et al. Antibody concentration and clinical protection after Hib conjugate vaccine in the United Kingdom. JAMA 2000; 284: 2334–40.
26. Wenger J. Epidemiology of Haemophilus influenzae type b disease and impact of Haemophilus influenzae type b conjugate vaccines in the United States and Canada. Pediatr Infect Dis J 1998; 17: S132–6.
27. Moulton LH, Chung S, Croll J, Reid R, Weatherholtz RC, Santosham M. Estimation of the indirect effect of Haemophilus influenzae type b conjugate vaccine in an American Indian population. Int J Epidemiol 2000; 29: 753–6.
28. Sarangi J, Cartwright K, Stuart J, Brookes S, Morris R, Slack M. Invasive Haemophilus influenzae disease in adults. Epidemiol Infect 2000; 124: 441–7.
29. Bisgard KM, Kao A, Leake J, Strebel PM, Perkins BA, Wharton M. Haemophilus influenzae invasive disease in the United States, 1994-1995: near disappearance of a vaccine-preventable childhood disease. Emerg Infect Dis 1998; 4: 229–37.
30. Stoll B. The global impact of neonatal infection. Clin Perinatol 1997; 24: 1–21.
31. Zangwill K, Schuchat A, Wenger J. Group B streptococcal disease in the United States, 1990: report from a multistate active surveillance system. MMWR CDC Surveill Summ 1992; 41 (SS-6): 25–32.
32. Centers for Disease Control and Prevention. Decreasing incidence of perinatal group B streptococcal disease—United States, 1993-1995. MMWR Morb Mortal Wkly Rep 1997; 46: 473–7.
33. Schuchat A. Group B streptococcus. Lancet 1999; 353: 51–6.
34. Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease: a public health perspective. MMWR Morb Mortal Wkly Rep 1996; 45 (RR-7): 1–24.
35. Schrag SJ, Zywicki S, Farley MM, Reingold AL, Harrison LH, Lefkowitz LB, et al. Group B streptococcus disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med 2000; 342: 15–20.
36. Tyrrell GJ, Senzilet LD, Spika JS, Kertesz DA, Alagartnam M, Lovgren M, et al. Invasive disease group B streptococcal infection in adults: results from a Canadian, population-based, active laboratory surveillance study – 1996. J Infect Dis 2000; 182: 168–73.
37. Schwartz B, Schuchat A, Oxtoby M, Cochi S, Hightower A, Broome CV. Invasive group B streptococcal disease in adults. A population-based study in metropolitan Atlanta. JAMA 1991; 266: 1112–4.
38. Farley MM, Harvey RC, Stull T, Smith JD, Schuchat A, Wenger JD, et al. A population-based assessment of invasive disease due to group B streptococcus in nonpregnant adults. N Engl J Med 1993; 328: 1807–11.
39. Blumberg HM, Stephens DS, Modansky M, Erwin M, Elliot J, Facklam RR, et al. Invasive group B streptococcal disease: the emergence of serotype V. Infect Dis J 1996; 173: 365–73.
40. Jackson L, Hilsdon R, Farley M, Harrison L, Reingold A, Plikaytis B, et al. Risk factors for group B streptococcal disease in adults. Ann Intern Med 1995; 123: 415–20.
41. Robbins J, Scheerson R, Vann W, Bryla D, Fattom A. Prevention of systematic infections caused by serogroup B streptococcus and Staphylococcus aureus by multivalent polysaccharide protein conjugate vaccines. Ann NY Acad Sci 1995; 754: 68–82.
42. Baker CJ, Paoletti LC, Wessels MR, Guttormsen HK, Rench MA, Hickman ME, et al. Safety and immunogenecity of capsular polysaccharide-tetanus toxoid conjugate vaccines for group B streptococcal type Ia and Ib. J Infect Dis 1999; 179: 142–50.

43. Ciesielski CA, Hightower AW, Parsons SK, Broome CV. Listeriosis in the United States: 1980-1982. Arch Intern Med 1988; 148: 1416–9.
44. Schuchat A, Deaver K, Wenger J, Plikaytis B, Mascola L, Pinner R, et al. Role of foods in sporadic listeriosis. I. Case-control study of dietary risk factors. JAMA 1992; 267: 2041–5.
45. Tappero JW, Schuchat A, Deaver KA, Mascola L, Wenger JD. Reduction in the incidence of human listeriosis in the United States. JAMA 1995; 273: 1118–22.
46. Centers for Disease Control and Prevention. Multistate outbreak of listeriosis – United States, 1998. MMWR Morb Mortal Wkly Rep 1998; 47: 1085–6.
47. Pennington T. The microbiological safety of food. J Med Microbiol 2000; 49: 677–9.
48. Schuchat A, Swaminathan B, Broome C. Epidemiology of human listeriosis. Clin Microbiol Rev 1991; 4: 169–83.
49. Fraser DW, Darby CP, Koehler R, Jacobs CF, Feldman RA. Risk factors bacterial meningitis: Charleston County, South Carolina. J Infect Dis 1973; 127: 271–7.
50. Fraser DW, Henke CE, Feldman RA. Changing patterns of bacterial meningitis in Olmsted County, Minnesota, 1935-1970. J Infect Dis 1973; 128: 300–7.
51. Davey P, Cruikshank J, McManus I, Mahood B, Snow M, Geddes A. Bacterial meningitis—ten years experiences. J Hyg Camb 1982; 88: 383–401.

Submitted September 3, 2001; accepted November 15, 2001

Au/Ed: See Query Sheet

Scand J Infect Dis 34: 00–00, 2002

Taylor & Francis healthsciences

Prevalence of Penicillin Non-susceptible Invasive Pneumococcal Disease in the Elderly in Scotland, 1992–99

MOE H. KYAW[1,2], IAN G. JONES[2] and HARRY CAMPBELL[1]

From the [1]Public Health Sciences, University of Edinburgh, Edinburgh, UK, [2]Scottish Centre for Infection and Environmental Health, Glasgow, UK

Penicillin resistance of Pneumococci is a problem in several European countries. Therefore, we examined 510 invasive pneumococcal isolates, collected between 1992 and 1999 via a national network of diagnostic laboratories covering the entire population of Scotland, for penicillin susceptibility, in order to determine the prevalence, site of infection and serogroup/type distribution of penicillin-resistant Pneumococci in the elderly (≥ 65 y). Of the 510 isolates, 91.6% ($n = 467$) were from blood, 4.7% ($n = 24$) from other sterile sites and 3.7% ($n = 19$) from cerebrospinal fluid. The prevalence of penicillin non-susceptible isolates during the study period was 9%. An increase in the proportion of Pneumococci non-susceptible to penicillin was detected from 1996 onwards, from 10.8% in 1996 to 14.3% in 1999. There were 2 isolates with high-level penicillin resistance, both of which were of serotype 14, accounting for 4.3% (2/46) of all non-susceptible isolates. Penicillin non-susceptible isolates belonged to the following serogroups: 14 (32.6%); 9 (30.4%); 6 (19.6%); 23 (10.9%); and 19 (6.5%). The leading non-susceptible serotype/group varied according to the specimen type: serotype 14 for blood and serogroup 9 for all other sterile sites. Current polysaccharide and new 7-, 9- and 11-valent conjugate vaccine formulations included the serogroups responsible for all the penicillin non-susceptible isolates detected. Therefore vaccination represents the most effective strategy for decreasing the burden of drug resistance. Constant surveillance of the patterns of antibiotic non-susceptible isolates, the site of infection and the serogroup/type are necessary in order to select antibiotic therapy and establish vaccination policy for the prevention of invasive pneumococcal disease.

M.H. Kyaw, Scottish Centre for Infection and Environmental Health, Clifton House, Clifton Place, Glasgow G3 7LN, UK. Tel.: +44 141 300 1184; Fax: +44 141 300 1170; E-mail: moe.kyaw@scieh.csa.scot.nhs.uk

INTRODUCTION

Pneumococci are responsible for a substantial burden of disease in the elderly, resulting in hospitalization, disease complications and death. The incidence rate of invasive pneumococcal disease is estimated to be between 45 and 90 per 100,000 persons aged ≥ 65 y (1). Compared with other age groups, the case-fatality rate of pneumococcal disease is higher in the elderly, being 20–40% (2–4). The prevalence of Pneumococci resistant to penicillin and other antibiotics is increasing globally (5) and this complicates the treatment of invasive pneumococcal disease, particularly meningitis (6).

The rate of drug-resistant isolates varies with the geographic location (7) and the age of the patient, being more common in children than adults (8). Although extensive data exist concerning rates of drug resistance in young children, little is known about the level of drug resistance in the elderly in Scotland and most other parts of the world. Data from the US indicate that the prevalence of drug-resistant Pneumococci in the elderly was $\approx 15\%$ in 1995–96 and has been increasing in recent years (9). In some parts of the US, up to 40% of invasive isolates have shown reduced susceptibility to penicillin. Therefore, we decide to review laboratory reports of penicillin non-susceptible invasive pneumococcal disease collected via a national network of diagnostic laboratories covering the entire population of Scotland during the period 1992–99, in order to estimate the magnitude of this problem in the elderly population.

METHODS AND MATERIALS

Isolates from patients with pneumococcal disease tested for penicillin susceptibility were identified from laboratory reports received at the Scottish Centre for Infection and Environmental Health (SCIEH) and the Scottish Meningococcus and Pneumococcus Reference Laboratory (SMPRL). The SMPRL provides a national service for culture confirmation, serogrouping/typing and antimicrobial susceptibility of Pneumococci and Meningococci to all 32 diagnostic laboratories in Scotland. It was established in 1992 for the purpose of monitoring the epidemiological characteristics of pneumococcal and meningococcal disease in Scotland. All diagnostic laboratories in Scotland are encouraged to send all invasive pneumococcal isolates to the SMPRL for serotyping and antibiotic susceptibility testing. However, the referral pattern is likely to vary among participating laboratories. Therefore, enhanced pneumococcal surveillance was established in November 1999 with the aim of producing an improved pneumococcal dataset for the periods before and after the introduction of conjugate vaccine in the UK.

In this study we only included isolates from sterile samples, such as blood, cerebrospinal fluid (CSF), joint and pleural fluids. Duplicate isolates from the same patient were excluded from the study. Pneumococci isolated from these sterile sites were regarded as evidence of invasive disease. During the study period, the elderly population (≥ 65 y) of Scotland comprised $\approx 15.3\%$ (784,141/5,120,000) of the entire population (10).

A latex agglutination test was used to identify Pneumococci (11). Serotying was done on the basis of capsular swelling with type-specific antisera obtained from the Statens Serum Institut (Copenhagen, Denmark). Penicillin susceptibility testing was performed using the E-test (Cambridge Diagnostics, Cambridge, UK). The breakpoints for penicillin susceptibility were defined in accordance with the recommendations of the NCCLS (12). Penicillin sensitivity, intermediate resistance and high-level resistance were defined if

DOI: 10.1080/00365540210147534

13c

isolates had MICs of ≤ 0.06, 0.1–1 and ≥ 2 µg/ml, respectively. Intermediately and high-level resistant isolates were considered as non-susceptible isolates.

Data concerning the annual doses of penicillin dispensed in Scotland between 1992 and 1999 were obtained from the Primary Care Unit, Information and Statistics Division, National Health Service, Scotland. The SPSS software program (Version 10) was used for data analysis. Pearson correlation was used to determine the association between the annual prevalence of penicillin-resistant isolates and the number of penicillin doses dispensed in Scotland between 1992 and 1999. The 1996 mid-year population figure was used to calculate the overall incidence rate of invasive disease. Annual rates of antibiotic prescriptions per 100 population were calculated for penicillin, erythromycin and all antibiotics for 1992–99.

RESULTS

Between 1992 and 1999, 510 invasive isolates were tested for penicillin susceptibility from the elderly: 46.3% ($n = 236$) were from males, 53.5% ($n = 273$) from females and in 0.2% ($n = 1$) the gender was unknown. The mean age of the subjects was 77 y (range 65–98 y). Of the 510 isolates, 91.6% ($n = 467$) were from blood, 4.7% ($n = 24$) from other sterile sites and 3.7% ($n = 19$) from CSF (Table I). There was a steady increase in the number of blood cultures during the study period. The ratio of positive blood to positive CSF cultures increased from 23:1 in 1992 to 67:1 in 1999. The overall incidence of invasive pneumococcal disease was 11.3 per 100,000 population during 1992–99 (range 8.6–12.6).

Proportion of penicillin non-susceptible isolates

The prevalence of penicillin non-susceptible isolates ranged from 2.6% to 14.7% during 1992–99 (Fig. 1). There was no increase in the prevalence of penicillin non-susceptible isolates between 1992 and 1995, in contrast to the increasing proportion of these isolates found from 1996 onwards. A similar trend was also observed for the age groups ≤ 5 y and 5–64 y. Overall, the rate of non-susceptible isolates in the elderly during 1992–99 was 8.6%, which was similar to that in the age group 5–64 y (7.3%) but substantially higher than that in the age group ≤ 5 y (3.7%). The annual prevalence of non-susceptible isolates in the elderly was consistently higher than that in the age group ≤ 5 y. The annual rate of non-susceptible isolates in the elderly was also higher than that in the age group 5–64 y, except for the years 1996 and 1998. Rates of antibiotic prescriptions per 100 population ranged from 230–272 for penicillin, 51–79 for erythromycin and 365–485 for all antibiotics during 1992–99.

There was a significant correlation between the prevalence of penicillin non-susceptible isolates and the rates of penicillin, erythromycin and all antibiotic prescriptions dispensed in Scotland between 1992 and 1999 for the age groups ≤ 5 y ($p = 0.004$, 0.002 and 0.009, respectively) and ≥ 65 y ($p = 0.021$, 0.026 and 0.013, respectively). A statistically significant correlation was noted between penicillin non-susceptibility and the prescription rate for erythromycin ($p = 0.013$), but not for penicillin ($p = 0.153$) or all antibiotics ($p = 0.056$), in the age group 5–64 y.

Non-susceptible serogroups/types

The distribution of penicillin non-susceptible serogroups/types by specimen type is shown in Table I. The most common serogroups/types were 14 (32.6%; 15/46), 9 (30.4%; 14/46), 6 (19.6%; 19/46), 23 (10.9%; 5/46) and 19 (6.5%; 3/46). These 5 serogroups/types accounted for all the non-susceptible isolates. Serotype 14 was responsible for high-level resistance, accounting for 4.3% (2/46) of non-susceptible isolates. The main non-susceptible serogroup/type also varied with the source of the specimen: serotype 14 from blood and serogroup 9 from other sterile sites. There were no non-susceptible isolates from CSF (Table I).

Vaccine coverage

The coverage of 7–11-valent conjugate vaccine and the 23-valent polysaccharide vaccine were both 100% for penicillin non-susceptible pneumococcal isolates (Table II).

DISCUSSION

An increase in the prevalence of penicillin non-susceptible Pneumococci has been detected in the Scottish elderly in recent years. Although not consistent, an increase in the rate of non-susceptibility in the age groups ≤ 5 y and 5–64 y was also observed after 1996. Although the reason for this is not clearly understood, the introduction of a new blood culture system (BacTAlert) in 1996 and the increase in blood cultures taken from febrile patients may be partly responsible (13). A 3-fold increase in the ratio of positive blood to positive CSF cultures during the study period would tend to support these explanations. However, our findings are likely to be biased owing to the voluntary referral for testing of penicillin susceptibility and variations in referring invasive pneumococcal isolates to the SMPRL among diagnostic laboratories in Scotland.

It is also possible that non-susceptible isolates were more likely to be submitted if they were from patients with treatment failure. In addition, the primary laboratory may be more likely to refer for confirmation non-susceptible isolates which have already been tested for susceptibility. The prevalence of penicillin non-susceptible isolates was lower in subjects aged ≤ 5 y than in those aged ≥ 65 y. This suggests that the reporting of invasive isolates is likely to be affected by age. Thus these data should be interpreted with caution. Nevertheless, they indicate the extent of penicillin non-susceptible pneumococcal disease among the elderly. US data show that penicillin-resistant Pneumococci are increasing in prevalence (9) and are more often likely to be resistant to other antibiotics (14). This rise in non-susceptible isolates limits the choice of empirical therapy in the elderly, who are at the greatest risk of death and the complications of pneumococcal disease. Although the clini-

Table I. *Distribution of penicillin non-susceptible isolates in the elderly in Scotland, 1992–99*

Serogroup	No. of isolates: Penicillin-susceptible	Penicillin-intermediately resistant	Penicillin-resistant	Total	
Blood					
1	28	–	–	28	
2	4	–	–	4	
3	42	–	–	42	
4	35	–	–	35	
6	29	8	–	37	
7	15	–	–	15	
8	22	–	–	22	
9	35	10	–	45	
10	7	–	–	7	
11	10	–	–	10	
12	10	–	–	10	Range
13	2	–	–	2	
14	58	12	2	72	
15	7	–	–	7	
17	1	–	–	1	
18	3	–	–	3	
19	46	2	–	48	
20	10	–	–	10	
21	1	–	–	1	
22	14	–	–	14	Range
23	33	4	–	37	
24	1	–	–	1	
31	3	–	–	3	
33	4	–	–	4	
34	2	–	–	2	
35	1	–	–	1	
38	4	–	–	4	
41	1	–	–	1	
42	1	–	–	1	
Total	429	36	2	467	
CSF					
3	2	–	–	2	
4	1	–	–	1	
6	1	–	–	1	
7	1	–	–	1	Range
8	1	–	–	1	
11	2	–	–	2	
12	1	–	–	1	
14	1	–	–	1	
16	1	–	–	1	
18	1	–	–	1	
19	2	–	–	2	
23	3	–	–	3	
24	2	–	–	2	
Total	19	–	–	19	
Other sterile sites[a]					
1	3	–	–	3	
3	5	–	–	5	
4	1	–	–	1	
6	–	1	–	1	
9	1	4	–	5	
14	2	1	–	3	
15	1	–	–	1	
19	1	1	–	2	
23	2	1	–	3	
Total	16	8	–	24	

[a] Isolates from pleural aspirate, pericardial fluid, lung aspirate, bronchial aspirate and bone marrow.

(b) antibiotic susceptible and non-susceptible pneumococcal disease.

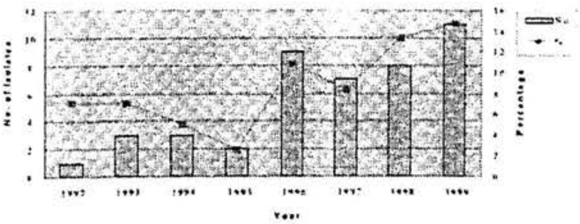


Fig. 1. Prevalence of penicillin non-susceptible pneumococcal isolates in the elderly in Scotland, 1992–99.

cal outcomes of non-susceptible pneumococcal disease have not been fully characterized, recent US data reveal that high-level penicillin-resistant invasive pneumococcal disease (MIC ≥ 2.0 mg/ml) is associated with increased mortality (15). Patients infected with penicillin non-susceptible Pneumococci (mainly intermediately resistant) are also reported to have worse medical outcomes (16) and a longer duration of hospitalization (3.7 d) compared to patients infected with penicillin- susceptible Pneumococci (4). These data highlight the need to minimize the impact of drug-resistant Pneumococci in Scotland. Improved surveillance for drug resistance, promotion of the judicious use of antibiotics and improved use of pneumococcal vaccine are key strategies in order to limit the spread of drug resistance (17). In the present study, the annual prevalence of penicillin non-susceptible isolates ~~did not correlate with the annual number of doses of penicillin dispensed in Scotland~~. The observed development of an increased rate of non-susceptible isolates is difficult to determine and may relate to the spread of drug-resistant clones (18). Studies on the molecular characterization of penicillin-resistant and multidrug-resistant pneumococcal isolates in Scotland are necessary to establish this.

Data on the prevalence of resistance, site of infection and serogroup/type distribution can inform antibiotic treatment decisions. Treatment failures have been observed in patients with penicillin-resistant strains (MIC $\geq$ 0.12 mg/ml) causing meningitis (19, 20). In the present study, no isolates from CSF were non-susceptible to penicillin. Previous data indicate that serotype 3 is associated with a high case-fatality rate (21). We found that serotype 3 was the third most common serotype isolated from blood specimens. Nevertheless, these isolates were uniformly susceptible to penicillin. Serogroups 6, 9, 14, 19 and 23 accounted for all cases of penicillin non-susceptibility in Scotland. The 2 high-level resistant isolates were found to be serotype 14. In the US, serotype 14 was reported to have caused an outbreak of multidrug-resistant meningitis in crowded facilities (22) and serotypes 23F, 6A and 6B were more likely to be resistant to penicillin (23). Studies have shown that these 5 serogroups are most commonly carried in the nasopharynx (24). Our data showed that the current formulations of polysaccharide and conjugate pneumococcal vaccines include all these penicillin non-susceptible serogroups and this highlights the importance of vaccination for the prevention of pneumococcal disease. New pneumococcal conjugate vaccines have been shown to reduce not only disease (25) but also nasopharyngeal carriage, particularly that associated with drug-resistant Pneumococci (26). Thus, the use of conjugate pneumococcal vaccine in the elderly is likely to affect the transmission and spread of drug-resistant Pneumococci in institutional settings such as nursing homes and geriatric wards. In addition, there is strong evidence that polysaccharide vaccine is 50–80% effective at preventing invasive disease (27). The increased use of this vaccine could prevent ~~not only pneumococcal disease but also antibiotic resistance~~ (28). Nevertheless, uptake of this vaccine in the elderly is low (29, 30) and should be increased in the UK and other developed countries.

(b)

CONCLUSION

Our data show an increase in the proportion of penicillin non-susceptible Pneumococci among the elderly. It is likely that this will result in increases in morbidity and mortality due to invasive pneumococcal disease in this age group. Vaccination is the most effective measure to prevent pneumococcal disease resistant to penicillin and other antimicrobial agents. Current polysaccharide and conjugate pneumococcal vaccines cover the serogroups responsible for penicillin non-susceptibility in the elderly in Scotland. Constant surveillance of the patterns of antibiotic non-susceptible isolates and the site of infection is necessary in order to select optimal antibiotic therapy for the management of invasive pneumococcal disease.

Table II. *Penicillin non-susceptible pneumococcal isolates covered by the vaccines*

Vaccine	Sensitive: *n* (%)	Intermediate: *n* (%)	Resistant: *n* (%)	Total: *n* (%)
7-valent	255/464 (54.6)	44/44 (100)	2/2 (100)	301/510 (59.0)
9-valent	286/464 (61.6)	44/44 (100)	2/2 (100)	332/510 (65.1)
11-valent	351/464 (75.6)	44/44 (100)	2/2 (100)	397/510 (77.8)
23-valent	445/464 (95.9)	44/44 (100)	2/2 (100)	491/510 (96.3)

(a) correlated with the annual rate of penicillin dispensed for age groups, ≤ 5 years and ≥ 65 years but not 5-64 years in Scotland.

and Staff at the SMPRL

ACKNOWLEDGEMENT

The authors gratefully acknowledge the laboratory staff throughout Scotland for collecting the study data.

REFERENCES

1. Butler JC. Schuchat A. Epidemiology of pneumococcal infections in the elderly. Drugs Aging 1999: 15: 11–9.
2. Breiman R. Spika J. Navarro V. Darden PM. Darby CP. Pneumococcal bacteremia in Charleston County. South Carolina a decade later. Arch Intern Med 1990: 150: 1401–5.
3. Bennett N. Buffington J. LaForce M. Pneumococcal bacteraemia in Monroe County. New York. Am J Public Health 1992; 82: 1513–6.
4. Plouffe JF, Breiman RF, Facklam RR, et al. Bacteraemia with Streptococcus pneumoniae: implications for therapy and prevention. J Am Med Assoc 1996; 275: 194–8.
5. Jones R, Pfaller M. Bacterial resistance: a worldwide problem. Diagn Microbiol Infect Dis 1998: 31: 379–88.
6. Friedland I, McCracken G. Management of infections caused by antibiotic-resistant Streptococcus pneumoniae. N Engl J Med 1994; 331: 377–82.
7. Collingnon PJ. Turnidge JD. Antibiotic resistance in Streptococcus pneumoniae. Med J Aust (Suppl) 2000: 173: S58–64.
8. Klugman K. Pneumococcal resistance to antibiotics. Clin Microbiol Rev 1990: 3: 171–96.
9. Butler JC, Cetron MS. Pneumococcal drug resistance: the new "special enemy of old age". Clin Infect Dis 1999: 28: 730–5.
10. Information and Statistic Division. Scottish Health Statistic 1998. Edinburgh, UK: Information and Statistic Division, 1999.
11. Smart L. Serotying of Streptococcus pneumoniae strains by coagglutination. J Clin Pathol 1986; 39: 328–31.
12. NCCLS. Performance standards for antimicrobial susceptibility testing. 10th informational supplement. NCCLS document M100-S10. Villanova, PA: NCCLS. 2000.
13. Lagos R, Levine M. Prospective, population-based surveillance for ambulatory invasive pneumococcal disease in children in Santiago, Chile. 2nd International Symposium on Pneumococci and Pneumococcal Disease. Sun City, South Africa, 2000: Abstract 026.
14. Butler J, Hofmann J, Cetron M, Elliott J, Facklam R, Breiman R. The continued emergence of drug-resistant Streptococcus pneumoniae in the United States: an update from the Centres for Disease Control and Prevention's Pneumococcal Sentinel System. J Infect Dis 1996; 174: 986–93.
15. Feikin DR, Schuchat A, Kolczak M, Barrett NL, Harrison LH, Lefkowitz L, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995–1997. Am J Public Health 2000; 90: 223–9.
16. Metlay JP, Hofmann J, Cetron MS, Fine MJ, Farley MM, Whitney C, et al. Impact of penicillin susceptibility on medical outcomes for adult patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2000; 30: 520–8.
17. Jernigan D, Cetron M, Breiman R. Minimizing the impact of drug-resistant Streptococcus pneumoniae (DRSP): a strategy from the DRSP Working Group. J Am Med Assoc 1996; 275: 206–9.
18. McGee L, McDougal L, Zhou J, Spratt BG, Tenover FC, George R, et al. Nomenclature of major antimicrobial-resistant clones of Streptococcus pneumoniae defined by the pneumococcal molecular epidemiology network. J Clin Microbiol 2001; 39: 2565–71.
19. Parais MM, Ramilo O, McCracken GH. Management of meningitis caused by penicillin-resistant Streptococcus pneumoniae. Antimicrob Agents Chemother 1995; 39: 2171–5.
20. John C. Treatment failure with use of a third generation cephalosporin for penicillin-resistant pneumococcal meningitis: case report and review. Clin Infect Dis 1994; 18: 188–93.
21. Mufson M. Clinical aspects and importance of pneumococcal infections. Pathol Biol 1979; 27: 519–23.
22. Craig AS, Erwin PC, Schaaffner W, Elliott JA, Moore WL, Ussery XT, et al. Carriage of multi-resistant Streptococcus pneumoniae and impact of chemoprophylaxis during an outbreak of meningitis at a day care center. Clin Infect Dis 1999; 29: 1257–64.
23. Hofmann J, Cetron M, Farley M, et al. The prevalence of drug-resistant Streptococcus pneumoniae in Atlanta. N Engl J Med 1995; 333: 481–6.
24. Ghaffar F, Friedland IR, McCracken GH. Dynamics of nasopharyngeal colonization by Streptococcus pneumoniae. Pediatr Infect Dis J 1999; 18: 638–46.
25. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenecity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000; 19: 187–95.
26. Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman K. Immunogenecity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis 1999; 180: 1171–6.
27. MMWR. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunisation Practices (ACIP). MMWR Morb Mortal Wkly Rep 1997; 46 (RR-8): 1–24.
28. Butler JC, Dowell SF, Breiman RF. Epidemiology of emerging pneumococcal resistance: implications for treatment and prevention. Vaccine 1998; 16: 1693–7.
29. McDonald P, Friedman E, Banks A, et al. Pneumococcal vaccine campaign based in general practice. Br Med J 1997; 314: 1094–8.
30. Fedson DS. Pneumococcal vaccination in the United States and 20 other developed countries. Clin Infect Dis 1998; 26: 1117–23.

Submitted December 28, 2001; accepted April 30, 2002

Pneumococcal vaccination: opinion of general practitioners and hospital doctors in Scotland, 1999-2000

MH Kyaw, JC Bramley, J Chalmers, IG Jones, H Campbell

Summary: *A cross sectional survey by postal questionnaire was carried out to examine general practitioners' (GPs) and hospital doctors' (HDs) knowledge, attitudes and practice (KAP) with regard to pneumococcal vaccination in primary and hospital care in Scotland. Most GPs and HDs considered patients with chronic medical conditions, as recommended by the Department of Health (DoH), to be candidates for pneumococcal vaccination. Although the DoH does not currently recommend the vaccine for all the elderly, 47% of GPs and 46% of HDs reported that the vaccine should be given to this group. GPs (61-85%) and HDs (48-55%) indicated that they considered the vaccine to be safe and effective. The acceptance of pneumococcal vaccine was much lower than for influenza vaccine however, and 79% of HDs and 17% of GPs had never used the vaccine. Documented policies (with or without set targets) for pneumococcal vaccine existed in only 14% of general practice and 3% of hospital settings. Over 70% of respondents indicated that GPs should take responsibility for pneumococcal vaccination. The main sources of knowledge about pneumococcal vaccines were stated to be discussion with colleagues, review of medical literature, past experience, and the DoH recommendations. A clear immunisation policy and financial support for vaccination were identified as important strategies to improve pneumococcal vaccine coverage. Strategies directed toward these factors could enhance vaccine delivery and coverage of vaccine in high-risk individuals.*

Key words:
pneumococcal vaccine
influenza vaccine
immunisation policy
vaccine coverage
high-risk groups

Commun Dis Public Health 2001: 4: 42-48

Introduction

Pneumococcal disease is an important cause of hospitalisation and death in the United Kingdom (UK) and presents a significant public health problem[1]. The current 23-valent polysaccharide vaccine is safe, and is effective in preventing 50-80% of invasive pneumococcal disease[2,3]. This vaccine has, in addition, been shown to be cost-effective in the United States and Europe including the UK[4-6]. However, polysaccharide vaccine is ineffective in two year olds, the age group with the highest incidence of invasive and mucosal disease. This has led to the development of conjugate vaccines, one of which has been shown to be highly efficacious in preventing invasive disease (97.4%, 95% CI, 82.7-99.9) in infants[7]. It is under review for European licensure.

In the UK, pneumococcal polysaccharide vaccine is currently recommended for individuals aged two years and above with splenic dysfunction, chronic heart, lung, liver, and renal diseases, diabetes mellitus or immunocompromising conditions[8]. However, surveys in England have shown that only 4-15%, and 0.5% of people with these indications, had received the vaccine in primary and hospital care respectively[9,10]. It is clear that acceptance of pneumococcal vaccine among general practitioners (GPs) and hospital doctors (HDs) is low. We therefore conducted a survey of GPs and HDs in Scotland to examine their KAP in relation to pneumococcal vaccination in order to identify the barriers that may affect vaccine use.

Methods

In September 1999, a total of 800 GPs and HDs practising in Scotland were identified for the survey.

MH Kyaw, JC Bramley, IG Jones
Scottish Centre for Infection and Environmental Health

H Campbell
University of Edinburgh, Department of Public Health Sciences

J Chalmers
Information and Statistics Division of the Common Services Agency

Address for correspondence:
Moe H Kyaw:
Scottish Centre for Infection and Environmental Health
Clifton House
Clifton Place
Glasgow
G3 7LN
Tel. 0141 300 1184
Fax. 0141 300 1170
Email: Moe.Kyaw@scieh.csa.scot.nhs.uk

The Information and Statistics Division (ISD) of the Common Services Agency, Edinburgh, supplied the names of 400 GPs selected at random from a national register, together with associated demographic characteristics. The HDs were chosen by asking each of 30 NHS hospitals, selected to be representative of Scotland, to supply details (names, specialties, positions and corresponding addresses) of 25 medical doctors selected non-systematically from personal records. Four hundred doctors from 16 hospitals were surveyed. The study design and questionnaire was modified from that of Berk and colleagues[11]. A pilot study was conducted among 12 GPs and 12 HDs during October 1999 after which the questionnaire was amended as necessary. In November 1999, the revised questionnaire was sent to the 800 GPs and HDs with a reminder questionnaire sent to those who did not respond after six weeks. Participants were questioned about the target groups for vaccine, vaccine effectiveness, practice and policies, the source of their knowledge, and any initiatives in place to increase the use of pneumococcal vaccine in their setting.

Data analysis

Data analysis was performed using SPSS version 10. The chi-squared test was used to determine the significance of association between the variables for KAP of pneumococcal vaccination.

TABLE 1 Characteristics of questionnaire respondents

General practitioners (n=286)	Number	(%)
Patient population		
mean number of patients per practice	5127	
mean number of registered elderly patients (≥65 years) per practice	386	
Practice type		
group	239	(84)
single	47	(16)
Practice location		
rural	42	(15)
urban	244	(85)
Hospital doctors (n=198)	**Number**	**(%)**
Grades		
Consultant	39	(20)
Specialist Registrar	39	(20)
Registrar	42	(21)
Senior Registrar	40	(20)
House Officer	38	(19)
Specialties		
Cardiology	18	(9)
Respiratory medicine	20	(10)
Renal medicine	21	(10)
Endocrinology	23	(12)
Gastroenterology	21	(11)
Oncology	23	(12)
Accident and Emergency	27	(13)
Geriatric/ Elderly medicine	21	(11)
General medicine	24	(12)

Results

Of the 800 questionnaires, 504 (63%) were returned. Of these, 20 were unanswered because the intended recipient had moved or did not want to participate. Of the 484 (60%) completed questionnaires, 286 (59%) were from GPs and 198 (41%) were from HDs. Table 1 displays the characteristics of respondents by healthcare setting.

Pneumococcal vaccine: knowledge of target groups

The respondents' views on pneumococcal vaccination in various high-risk conditions are shown in Table 2. Splenic dysfunction was the condition most frequently agreed or strongly agreed to be an indication for pneumococcal vaccination by both GPs (99%) and HDs (81%). Vaccination of all elderly was least frequently considered as an indication by either GPs (47%) or HDs (46%). GPs were more likely than HDs to agree or strongly agree about the need for the vaccine in the high-risk conditions currently recommended for vaccination by the DoH. Compared to GPs, HDs were more likely to be uncertain whether the risk condition cited was an indication for vaccine recommendation.

Pneumococcal vaccine: knowledge of safety and effectiveness

A significant proportion of respondents did not know about pneumococcal vaccine safety and effectiveness for the patient categories given (Table 3). The proportion was much higher for HDs than GPs.

Pneumococcal vaccine: use

The majority of HDs (79%) had never used the vaccine compared with only 17% of GPs (figure 1). A statistical significance was not found for particular specialities or grades of HDs in their use of vaccine. General practice location and type were associated with vaccine use among GPs, with higher use by GPs in urban areas than rural areas (rural = 35/40 (88%) versus urban = 199/242 (82%), p = 0.55) and by group practices rather than single practices (group practices = 199/235 (85%) versus single practices = 35/47 (74%), p = 0.089).

FIGURE 1 Use of pneumococcal vaccine among respondents in the past year (GPs: n=282, HDs: n=196)

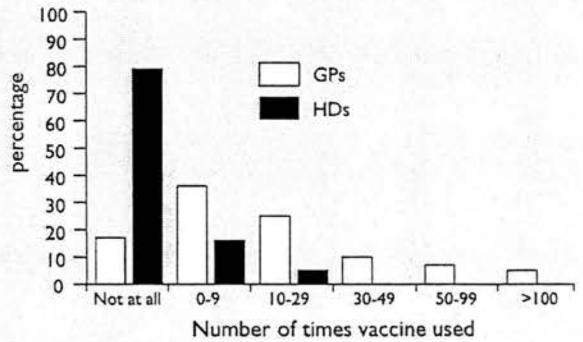


TABLE 2 Views of respondents on indications for pneumococcal vaccination in various high risk patient groups by level of agreement (%)* (GPs: n=286, HDs: n=198)

Risk conditions	Respondent	Strongly agree	Agree	Disagree	Strongly disagree	Don't know
Splenic dysfunction#	GPs	80	19	0	1	0
	HDs	67	14	2	1	16
Chronic pulmonary disease#	GPs	59	36	1	1	2
	HDs	34	40	5	1	20
Immunocompromised#	GPs	51	33	5	1	8
	HDs	36	32	6	3	22
Chronic heart disease#	GPs	39	39	11	1	9
	HDs	21	40	11	1	27
Chronic renal disease#	GPs	36	40	10	1	13
	HDs	20	35	10	1	33
Diabetes mellitus#	GPs	36	40	10	1	13
	HDs	14	38	15	1	32
Chronic liver disease#	GPs	30	39	13	1	16
	HDs	17	39	11	1	31
Elderly (≥65 years) (residents of long stay facility)	GPs	15	34	28	5	16
	HDs	13	39	18	3	25
All elderly ≥65 years	GPs	16	31	32	8	12
	HDs	10	36	22	4	27

* Not all categories add up to 100% due to incompete forms
# Currently recommended by the UK Departments of Health

TABLE 3 Views of respondents on the safety and effectiveness of pneumococcal vaccine in preventing invasive pneumococcal disease by patient group (%)* (GPs: n=286, HDs: n=198)

Risk conditions	Respondent	Strongly agree	Agree	Disagree	Strongly disagree	Don't know
Immunocompromised adults	GPs	28	46	5	2	18
	HDs	17	38	4	1	38
Adults with chronic heart/pulmonary /renal/liver/diabetic disease	GPs	25	60	3	1	11
	HDs	13	40	4	1	42
Elderly (≥65 years)	GPs	20	45	11	2	20
	HDs	12	36	6	2	43
Young adults	GPs	22	39	7	4	28
	HDs	16	34	7	3	40

Pneumococcal vaccine attitudes and practice

If an elderly patient specifically requested a vaccine to protect them against pneumonia, 53% of GPs and 41% of HDs answered they would use both influenza and pneumococcal vaccines. Influenza vaccine alone would be recommended by 40% of GPs and 36% of HDs (figure 2). GPs in urban areas were more likely to offer both influenza and pneumococcal vaccines (rural = 21/117 (18%) versus urban = 125/141 (89%), $p = 0.0001$), and those in rural areas were more likely to use influenza vaccine alone (rural = 96/117 (82%) versus urban = 16/141 (11%), $p = 0.0001$). Practice type was also related to use of vaccine. GPs in group

FIGURE 2 Response to elderly patients' requests for a vaccine against pneumonia (GPs: n=277, HDs: n=172)

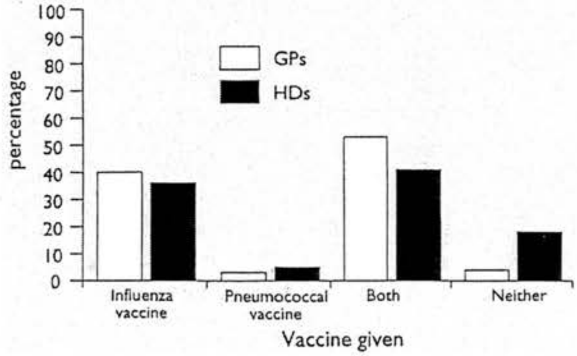


FIGURE 3 Reported pneumococcal vaccination policies (GPs: n=276, HDs: n=165)

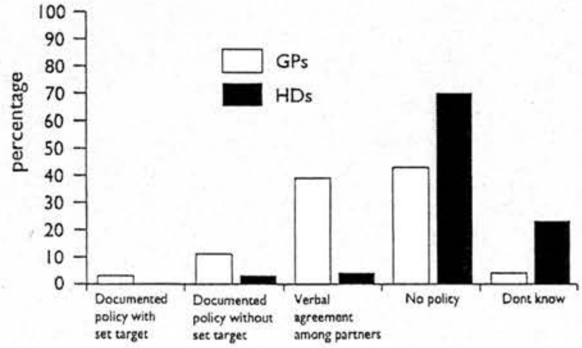


TABLE 4 Sources of knowledge about pneumococcal vaccine among respondents (GPs: n=562, HDs: n=368)

Source*	GPs	HDs
Discussion with colleagues	43	27
Own review of medical literature	38	33
Past experience	27	26
Department of Health	27	32
Health Boards	22	27
Further medical education	22	28
Advice from manufacture	14	5
Do not know	5	7

* can answer more than one source

practices were more likely to recommend influenza vaccine alone (group practices = 99/216 (46%) versus single practice = 13/42 (31%), p = 0.075) or both influenza and pneumococcal vaccine (group practices = 117/216 (54%) versus single practices = 29/42 (69%), p = 0.075) than those in single practices.

Pneumococcal vaccination policies

Figure 3 shows the policies for pneumococcal vaccination in the respondents' settings. There was no pneumococcal vaccination policy in the clinical setting of 70% of HDs and 43 % of GPs. Only 3% of GPs had a policy which included a set target. Very few HDs (3%) knew of a documented policy which existed in their clinical area, and none of these carried a set target.

Policies for pneumococcal vaccination were associated with general practice type and location, with GPs in urban areas (rural = 25/41 (61%) versus urban = 113/226 (50%), p = 0.19) and group practices (group practices = 124/229 (54%) versus single practices = 23/47 (49%), p = 0.51) more likely to have some form of pneumococcal vaccination policy than those in rural and single practices. No association was found in HDs' grades or specialties (data not shown).

Pneumococcal vaccination responsibilities

Figure 4 summarises the respondents' views on the primary responsibility for pneumococcal vaccination. Over 70% of GPs and HDs felt that the primary responsibility for pneumococcal vaccination lay with general practitioners, followed by the DoH and the Health Boards (HBs) and Health authorities (HAs).

FIGURE 4 Views on the primary responsibility for pneumococcal vaccination (GPs: n=478, HDs: n=356)

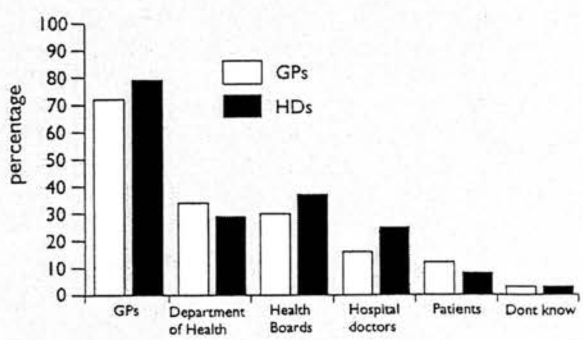


TABLE 5 Suggested strategies for improving pneumococcal vaccine coverage

Source*	GPs	HDs
A clear immunisation policy	87	80
Financial support for vaccination	72	54
Computerised systems to identify high risk patients	49	47
Vaccine awareness public health campaign	46	46
Further education on immunisation	32	44
Conclusive evidence of vaccine efficacy	22	30
Provision of a nurse assistant	18	16
Do not know	5	3

* can answer more than one source

Pneumococcal vaccine: source of knowledge

Discussion with colleagues, personal review of medical literature and past experience were the main sources for pneumococcal vaccine information among GPs and HDs. Consultants and specialist registrars mostly acquired information about pneumococcal vaccine from past experience and further education compared with HDs in other grades who stated other categories (see table 4).

Pneumococcal vaccine: strategies to improve the coverage

Eighty-seven percent of GPs and 80% of HDs believed that a clear vaccination policy would increase the coverage of vaccine in high-risk individuals. Financial support for pneumococcal vaccination was considered to be an important element in improving the vaccine coverage by both GPs (72%) and HDs (53%). Over 45% of both GPs and HDs considered that public health campaigns on pneumococcal vaccination and a computerised system to identify persons with definite indications for the vaccine would raise the vaccine coverage (table 5).

Discussion

Although pneumococcal polysaccharide vaccine has been licensed in the UK since 1979, information about the use of vaccine among GPs and HDs has not been available. To our knowledge, our data represent the first survey of the knowledge and reported pneumococcal vaccination practices of GPs and HDs in the UK. The sampling methods adopted and the good response rate from GPs and HDs suggest that these results may be representative of the GPs and HDs throughout Scotland.

Pneumococcal vaccine: knowledge and use

Our findings indicate that the majority of GPs and HDs support the use of vaccine in high-risk groups and recognise the safety and effectiveness of the vaccine. Surveys from the United States have also showed that physicians in general practice and hospital settings have adequate knowledge of pneumococcal vaccine target groups and its usefulness, but that they have failed to act on this in clinical practice[11-12]. Compared to GPs, HDs were less likely to know whether the vaccine was safe and effective in high-risk patients. Since many high-risk persons come into contact with HDs during their hospitalisations and out-patient visits, this lack of knowledge about pneumococcal vaccine could lead to missed opportunities for vaccination in hospital care.

It is clear from the survey that among both GPs and HDs acceptance of influenza vaccine was higher than of pneumococcal vaccine. Poor acceptance and low use of pneumococcal vaccine among GPs and HDs may have been influenced by a poor understanding of the burden of pneumococcal disease together with the inconclusive evidence from randomised trials of its efficacy in the elderly[15]. The factors accounting for poor use of pneumococcal vaccine in single practices and practices located in rural areas are not fully understood. Whether this is a result of greater workload or other factors is difficult to determine and requires further investigation.

As a result of this finding, further data on the number of patients with chronic heart disease and chronic obstructive pulmonary/lung disease in urban and rural areas were sought from the Continuous Morbidity Recording (CMR) system, ISD. The CMR system includes 53 general practices, more than 5% of the population of Scotland. The data from the CMR are considered to be representative of Scottish population in term of sex, age and geographic locations. The CMR data showed that there was a difference in the portion of patients with chronic heart disease (rural = 25/1,000 population versus urban = 21/1,000 population) and chronic pulmonary disease (rural = 57/1,000 population versus urban = 42/1,000 population) in rural versus urban areas (data obtained from Matthew Armstrong, ISD on 30/Jan/2001). This suggests that differences in KAP of pneumococcal vaccination in rural and urban area GPs are unlikely to be related to the proportion of such patients.

Evidence from the UK and North America suggests that acceptance of pneumococcal vaccination in high-risk persons increases when primary and secondary health care teams offer the vaccine[9,10,16,17]. A recent American survey found that the lack of a doctor's recommendation was the predominant reason for not receiving pneumococcal vaccine[18]. It is therefore important to educate all members of primary and secondary care teams regarding vaccine effectiveness and side effects, and the benefits of pneumococcal vaccination in high-risk persons. Although there is a considerable doubt on its efficacy in immunocompromised individuals[19], vaccination may be the most effective measure in this group with the highest incidence of invasive disease. Incorporating teaching on prevention of pneumococcal disease and an adult (as opposed to only childhood) vaccination programme in undergraduate and postgraduate medical training could not only increase the levels of knowledge and understanding of vaccination but also alter the attitudes and behaviour of doctors towards pneumococcal vaccination in the future.

Pneumococcal vaccine: source of information and policies

It appears that there is a need for more attention to be given to the promotion of recommendations on pneumococcal vaccination by the DoH and HBs/HAs since most GPs and HDs acquire this information from their own review of the medical literature. In addition, many practices and hospital care settings lacked clear pneumococcal vaccination policies. A review of pneumococcal vaccination policies in 21 countries suggests that specific recommendations and action by the health officials would play an important role in improving the use of pneumococcal vaccine[15]. Establishing appropriate guidelines, audit and feedback on performance may have a positive impact on improving coverage of pneumococcal vaccine in the future.

Pneumococcal vaccination: responsibilities and strategies

Since the target groups for influenza and pneumococcal vaccines overlap, offering pneumococcal vaccine to eligible persons when they attend for annual influenza vaccination could achieve a similar coverage for both (45%)[20]. This strategy has been strongly recommended by the DoH[8]. Our findings show that both GPs and HDs consider that the primary responsibility of pneumococcal vaccination should lie with GPs although a minority thought that this should be the DoH or HB/HA function. It is clear that collaboration and support from the DoH and HBs/HAs to GPs will be important in overcoming existing barriers.

HDs, nurses and pharmacists all play a vital role in improving the coverage of pneumococcal vaccine. Studies from the United States have shown that hospital-based pneumococcal vaccination programmnes during admissions or out-patient visits are an effective strategy for vaccinating high-risk persons[21,22]. Surveys have shown that 56-88% of pneumococcal vaccine eligible persons had previous hospital admissions[22-25]. Therefore, hospital based vaccination is a complementary strategy which should be considered in the UK.

About 85% of GPs and HDs suggested that financial support and incentive payments for pneumococcal vaccine could improve its use. At present, there is no payment mechanism for GPs regarding pneumococcal vaccination in Scotland. This clearly discourages the use of this vaccine by GPs. If funding were made available to establish target payments for adult vaccination as for childhood vaccination then the vaccine coverage would be likely to increase. The recent adoption of universal influenza vaccination in all elderly 65 years of age and above with a related payment scheme has been important step forward to improve the coverage of influenza vaccine[26]. Consideration should be given to extending this scheme to cover combined influenza and pneumococcal vaccine targets.

The need to identify and target eligible persons for pneumococcal vaccine with a computerised system was commented on by the majority of GPs and HDs. Studies from the United States have shown that a reminder system (with use of computer, chart and letter), standing orders for nurses and walk-in clinic produced an improvement in influenza and pneumococcal vaccines administration in the primary care and hospital care[16,27,28].

One American report highlighted that the lack of public awareness of indications for the vaccine was the major reason for not receiving the vaccine[18]. Most respondents in the present survey also felt that a public health campaign on pneumococcal vaccine awareness was important in improving the coverage of vaccine. One British report showed that such campaigns in general practices increased pneumococcal vaccine coverage from 4% to 33%[8]. Similar findings have been reported from the United States and Belgium[29-31].

In the present survey most GPs and HDs suggested that clear guidelines were essential to improve the coverage of vaccine. The current chronic disease-based pneumococcal vaccination policy needs to be made more precise so that specific indications of vaccination are given. In the United States, a specific objective has been set up to reach 80% coverage among high-risk persons by the year 2010[18]. A pneumococcal vaccination target does not yet exist in the United Kingdom.

American surveys showed that the majority of physicians believed pneumococcal vaccine should be given to elderly patients[11,12]. Our study found less support for vaccination of all elderly aged 65 years and above among GPs and HDs. In contrast to the American age-based policy, pneumococcal vaccination is not currently recommended for all elderly by the British DoH[8]. Economic studies have consistently shown that pneumococcal vaccination is cost effective or cost saving in the elderly[32]. Therefore, its routine use in the elderly should be reconsidered in the United Kingdom.

Our survey indicates that the majority of GPs and HDs have sufficient understanding and knowledge of pneumococcal vaccination. Compared to GPs, HDs were more likely to be uncertain about indications, safety and effectiveness of vaccine. No single factor appears to account for the low use of pneumococcal vaccine among GPs and HDs. The main barriers to improving the vaccine coverage are reported to be lack of clear immunisation policies and of financial support for adult vaccination. The results of this survey should provide relevant data to inform the development of future policies aiming to increase the coverage of pneumococcal vaccination among those recommended for vaccination in primary and hospital care settings.

Acknowledgements

We would like to thank the GPs and hospital doctors for their cooperation. We are indebted to Stuart Adams, Patricia Cassels, Matthew Armstrong, James McNally at the Scottish Centre for Infection and Environmental Health and the Information and Statistics Division, ISD in Scotland for their help and assistance in obtaining information and data entry.

References

1. MacFarlane J. The clinical impact of pneumococcal disease. In: Mayon-White RT, ed. The clinical impact of pneumococcal disease and strategies for its prevention. *Royal Soc Med Int Congress and Symp Series* 1995; **210**: London : Royal Society Medicine: 9-17.
2. Fedson DS. The clinical effectiveness of pneumococcal vaccination: a brief review. *Vaccine* 1999; **17**: S85-S90.
3. Hutchison BG, Oxman AD, Shannon HS, Lloyd S, Altmayer CA, Thomas K. Clinical effectiveness of pneumococcal vaccine. Meta-analysis. *Can Fam Physician* 1999; **45**: 2381-93.
4. Gable CB, Holzer SS, Engelhart L, Friedman RB, Smeltz F, Schroeder D, et al. Pneumococcal vaccine: efficacy and associated cost savings. *JAMA* 1990; **264**: 2910-5.
5. Sisk JE, Moskowitz AJ, Whang W, Lin JD, Fedson DS, McBean AM, et al. Cost-effectiveness of vaccination against pneumococcal bacteraemia among elderly people. *JAMA* 1997; **278**: 1333-9.
6. Ament A, Baltussen R, Duru G, Rigaud-Bully C, de Graeve D, Ortqvist A, et al. The cost effectiveness of pneumococcal vaccination for older people: a study in five western European countries. *Clin Infect Dis* 2000; **31**: 444-50.
7. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, et al. Efficacy, safety and immunogenecity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* 2000; **19**: 187-95.
8. Department of Health. *Immunisation against infectious disease*. London: HMSO, 1996.
9. McDonald P, Friedman E, Banks A, Anderson R, Carman V. Pneumococcal vaccine campaign based in general practices. *BMJ* 1997; **314**: 1094-8.
10. Kyaw MH, Nguyen-Van-Tam J, Pearson J. Family doctor advice is the main determinant of pneumococcal vaccine uptake. *J Epidemiol Community Health* 1999; **53**: 589-90.
11. Berk SL, Verghese A, Berk ML, Dison C, Smith K. Survey of physician acceptance of the pneumococcal vaccine. *South Med J* 1984; **77**: 450-4.
12. Patriarca PA, Schlech WF, Hinman AR, Conn JM, Gunn WJ. Pneumococcal vaccination practices among private physicians. *Public Health Reports* 1982; **97**: 406-8.
13. Rushton T, Ganguly R, Sinnott J, Banerji M. Barriers to immunization: an examination of factors that influence the application of pneumococcal vaccine by house staff. *Vaccine* 1994; **12**: 1173-9.
14. Noe CA, Markson LJ. Pneumococcal vaccination: perceptions of primary care physicians. *Prev Med* 1998; **27**: 767-72.
15. Fedson DS. Pneumococcal vaccination in the United States and 20 other developed countries, 1981-1996. *Clin Infect Dis* 1998; **26**: 1117-23.
16. Bloom H, Bloom J, Krasnoff L, Frank A. Increased utilization of influenza and pneumococcal vaccines in an elderly hospitalised population. *Am J Geriatr Soc* 1988; **36**: 897-901.
17. Centers for Disease Control (CDC). Adult immunisation: knowledge, attitudes, and practices – de Kalb and Fulton Countries, Georgia. *MMWR Morb Mortal Wkly Rep* 1988; **37**: 657-61.
18. Centers for Disease Control (CDC). Reasons reported by medicare beneficiaries for not receiving influenza and pneumococcal vaccination – United States. *MMWR* 1999; **48**: 886-90.
19. Jain A, Jain S, Grant V. Should patients positive for HIV infection receive pneumococcal vaccine? *BMJ* 1995; **310**: 1060-2.
20. Irish C, Alli M, Gilham C, Joseph C, Watson J. Influenza vaccine uptake and distribution in England and Wales,

July 1989 - June 1997. *Health Trends* 1998; **30**: 51-5.
21. Ratner ER, Fedson DS. Influenza and pneumococcal immunisation in medical clinics, 1978-1980. *Arch Intern Med* 1983; **143**: 2066-9.
22. Klein R, Adachi N. An effective hospital-based pneumococcal immunization program. *Arch Intern Med* 1986; **146**: 327-9.
23. Fedson D, Chairello L. Previous hospital care and pneumococcal bacteraemia: importance for pneumococcal immunization. *Arch Intern Med* 1983; **143**: 885-9.
24. Klein R, Adachi N. Pneumococcal vaccine in the hospital: improved use and implications for high-risk patients. *Arch Intern Med* 1983; **143**: 1878-81.
25. Magnussen CR, Valenti W, Mushlin A. Pneumococcal vaccine strategy: feasibility of a vaccination program directed at hospitalized and ambulatory patients. *Arch Intern Med* 1984; **144**: 1755-7.
26. Chief Medical Officer (CMO). Major changes to the policy on influenza immunisation. *CMO's update* 2000; **26**: 1.
27. Schreiner DT, Petrusa ER, Rettie CS, Kluge RM. Improving compliance with preventive medicine procedures in a house staff training. *South Med J* 1988; **81**: 1553-7.
28. Nichol K. Long term success with the national health objective for influenza vaccination. *J Gen Intern Med* 1992; **7**: 595-600.
29. MMWR. Pneumococcal immunization program – California, 1986-1988. *MMWR Morb Mortal Wkly Rep* 1989; (38): 517-9.
30. Campbell JF, Donohue MA, Nevin-Woods C, McBean AM. Pace NE, Williams WW, et al. The Hawaii pneumococcal disease initiative. *Am J Public Health* 1993; **83**: 1175-6.
31. Peetermans WE, Lacante P. Pneumococcal vaccination by general practitioners: an evaluation of current practice. *Vaccine* 1999; **18**: 612-7.
32. Fiebach N, Beckett W. Prevention of respiratory infections in adults. Influenza and pneumococcal vaccines. *Arch Intern Med* 1994; **154**: 2545-57.

ELSEVIER

Vaccine 20 (2002) 2516–2522

Vaccine

www.elsevier.com/locate/vaccine

Influenza and pneumococcal vaccination in Scottish nursing homes: coverage, policies and reasons for receipt and non-receipt of vaccine

Moe H. Kyaw [a,b,*], Beverley Wayne [b], Eileen M. Holmes [a,c], Ian G. Jones [b], Harry Campbell [a]

[a] *Department of Public Health Sciences, University of Edinburgh, Edinburgh, UK*
[b] *Scottish Centre for Infection and Environmental Health, Clifton House, Clifton Place, Glasgow G3 7LN, UK*
[c] *Department of Statistics of Statistics and Modelling Science, University of Strathclyde, Glasgow, UK*

Received 20 November 2001; received in revised form 25 February 2002; accepted 11 March 2002

Abstract

A national survey was carried out to determine the coverage of influenza and pneumococcal vaccines, policies, reasons for receipt, non-receipt of vaccine and strategies to improve vaccine coverage in Scottish nursing homes. Of the 550 nursing homes, 72% (394) participated in the study. Overall coverage was 85% for influenza vaccine in 2001–2002 season and 11% for pneumococcal vaccine in the last 5-year period. Only 6% (23/394) of homes were reported to have a systematic immunization record. The most frequently stated reasons for improved coverage of both vaccines were clear immunization policies (76%), awareness and education for staff and residents (68%), and consent on behalf of the incompetent residents (66%). The presence of vaccination policies was higher for influenza vaccine than pneumococcal vaccine expressed as verbal agreement (27% versus 3%), written policies with set target (24% versus 5%) and written policies without set target (17% versus 2%). Advice from the members of the community health care team was the principal reason for the receipt of both vaccines. The predominant reasons for non-receipt of vaccine were refusal by residents and family members (both vaccines) and lack of advice from general practitioners (pneumococcal vaccine). The substantial disparity in coverage of influenza and pneumococcal vaccine reflects the lack of national recommendations and policies for reimbursements for pneumococcal vaccination. These data suggest that greater efforts are needed to improve prevention behaviors of health care professionals and the public, organized vaccine delivery strategies and systematic vaccination documents to increase influenza and pneumococcal vaccination rates in nursing homes and other long-term care facilities. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Scottish nursing homes; Influenza and pneumococcal vaccination; Policies

1. Introduction

The elderly are at-risk of influenza and pneumococcal disease. Most elderly living in nursing homes have chronic medical conditions [1], and therefore have higher risk of complications and mortality from influenza and pneumococcal disease than the elderly living in the community [2–4]. Outbreaks of influenza and pneumococcal disease have been well documented in nursing homes [5–7]. In addition, data from the US shows that the prevalence of drug resistant pneumococci is increasing in the elderly [8]. Drug resistant pneumococcal strain (serotype 23) has been reported as a cause of an outbreak of pneumococcal disease in a nursing home with low vaccine coverage [6].

Susceptibility to infection and transmission of influenza and pneumococcal disease can be prevented by vaccination [9,10]. Studies show that the estimated effectiveness of influenza vaccine is 43–55% against pneumonia [9] and >42% against influenza-like illness [11] among elderly nursing home residents. Pneumococcal vaccine is 61–75% effective in preventing bacteraemia or meningitis in the elderly [12,13]. The administration of both vaccines is also considered cost-effective in the elderly [14–16]. Despite this evidence, influenza and pneumococcal vaccines are underused in the UK [17,18]. Influenza vaccination is currently targeted to all elderly (aged 65 years and above) and residents in long-term care facilities. However, pneumococcal vaccination is not yet recommended for these groups in the UK [19]. There are limited data on coverage and polices of influenza and pneumococcal vaccinations in UK nursing homes. In addition, little is known of the reasons for receipt and non-receipt of these vaccines in elderly nursing home residents. We therefore report national coverage of and policies for influenza and pneumococcal vaccines together with the factors which may be associated with the use and receipt of both vaccines in Scottish nursing homes. These data

* Corresponding author. Tel.: +44-141-300-1184; fax: +44-141-300-1170.
E-mail address: moe.kyaw@scieh.csa.scot.nhs.uk (M.H. Kyaw).

PII: S0264-410X(02)00177-9

could help to develop strategies to improve coverage of influenza and pneumococcal vaccines in nursing homes and other long-term care facilities.

2. Methods

A list of nursing homes and their addresses was obtained from the Information and Statistics Division (ISD) of the Common Services Agency of the National Health Service (NHS), Scotland. In 2001, there were 550 licensed nursing homes in the whole of Scotland, which provided nursing care primarily to the elderly population. A postal questionnaire was sent to each nursing home on 12 June 2001 with a request for it to be completed by the nurse in charge or care manager. A reminder was posted to non-respondents on 2 August 2001. The questionnaire requested information on the number of residents, the number of general practices looking after residents, the existence of immunization record, the number of residents receiving influenza vaccine or pneumococcal vaccine or both vaccines, vaccination policies, the factors associated with improved vaccine coverage and the reasons for receipt and non-receipt of vaccine, selected from a number of key reasons defined in a pilot study. Information was requested as aggregated format. Therefore, data are completely anonymous and do not identify individual elderly living in each nursing home. Information was entered in DataEase version 4.5 and data analyses were carried out in SPSS version 10 and Stata (Stata Corporation, version 6.0, 1999, College Station, Texas). Since the data are non-normally distributed, non-parametric tests were applied. Mann–Whitney tests were used to compare median coverage where the covariate binary and Kruskal–Wallis tests were used when the covariate had more than two levels.

3. Results

Of the 550 nursing homes, 394 homes (72%) responded to the questionnaire. The mean size of home was 46 residents. The number of general practices looking after residents ranged from 1 to 24 practices per nursing home (mean = 5). A systematic immunization record, which was defined as complete documentation of immunization history, existed in 6% (23/394) of nursing homes.

No significant differences in median influenza vaccination rates were found for the following covariates: areas of Scotland by Health Boards ($P = 0.37$), the presence of systematic immunization record ($P = 0.47$), the number of GPs per home (<5 GPs = 88% versus >5 GPs = 89%, $P = 0.69$). Similar results were obtained for the pneumococcal vaccine ($P = 0.37$, 0.55 and <5 GPs = 0% versus >5 GPs = 0%, $P = 0.10$, respectively). The number of residents was found to significantly affect the median coverage of influenza vaccination (<30 residents = 89% versus 31–50 residents = 90% versus >51 residents = 85%, $P = 0.007$) although this association was not observed in pneumococcal vaccination rates ($P = 0.71$). Nursing home with a pneumococcal vaccine policy had significantly higher median coverage rates of this vaccine than those who did not ($P = 0.007$). However, the presence of an influenza vaccination policy appeared to have no association with influenza vaccine coverage ($P = 0.54$).

4. Vaccine coverage

Although 394 returned the questionnaire, information on vaccine coverage of influenza and pneumococcal vaccinations was provided by 328 homes and 142 homes, respectively. Thus, vaccine coverage was calculated based on the appropriate denominators. Overall vaccine coverage was 85% for enfluenza vaccine in 2001–2002 season and 11% for pneumococcal vaccine in the last 5 years among 13,700 residents. Coverage of influenza and pneumococcal vaccines in residents by nursing home is shown in Table 1. Coverage of influenza vaccine was >70% of residents in 85% of nursing homes. The majority of nursing homes (74%) had less than 5% pneumococcal vaccine coverage among their residents.

5. Factors suggested for improving vaccine coverage

The most frequently reported reasons for improving coverage of both vaccines were a clear immunization policy

Table 1
Influenza and pneumococcal vaccine coverage among nursing homes which provided information on vaccination

Percentage of residents received	No. of nursing homes with vaccine coverage (%)
Influenza vaccine	
<40	8 (2)
40–49	5 (2)
50–59	12 (4)
60–69	26 (8)
70–79	36 (11)
80–89	86 (26)
90–99	97 (30)
100	59 (18)
Total	328 (100)
Mean	– (85)
Median	– (88)
Pneumococcal vaccine	
<5	105 (74)
5–9	11 (8)
10–19	8 (6)
20–49	6 (4)
>50	12 (8)
Total	142 (100)
Mean	– (11)
Median	– (0)

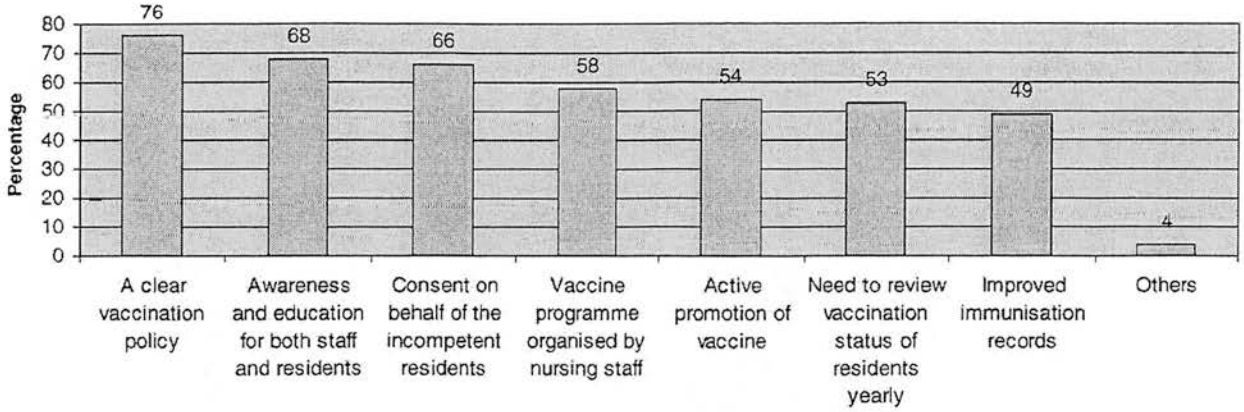


Fig. 1. Factors which could improve coverage of influenza and pneumococcal vaccine.

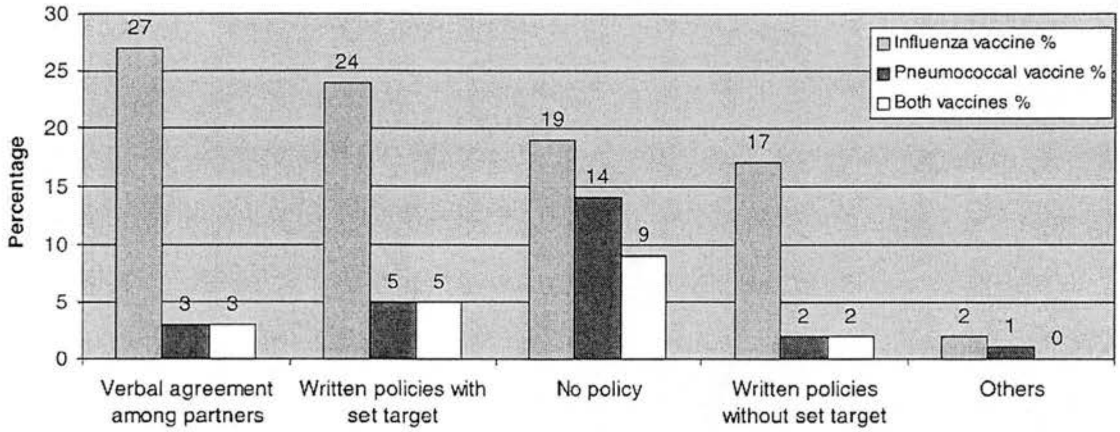


Fig. 2. Policies for vaccination of influenza, pneumococcal and both vaccines.

(76%), awareness and education for staff and residents (68%) and consent on behalf of the incompetent residents (66%) (Fig. 1). Other reported factors associated with vaccinations were organized vaccine programs by nursing staff, active promotion of vaccine, annual review of vaccination status and improved immunization records.

6. Vaccination policies

Of the respondents (394 homes), 68% ($n = 260$), 10% ($n = 42$) and 10% ($n = 42$) of nursing homes had one form of vaccination policies for influenza, pneumococcal or both vaccines, respectively. The presence of policies for influenza

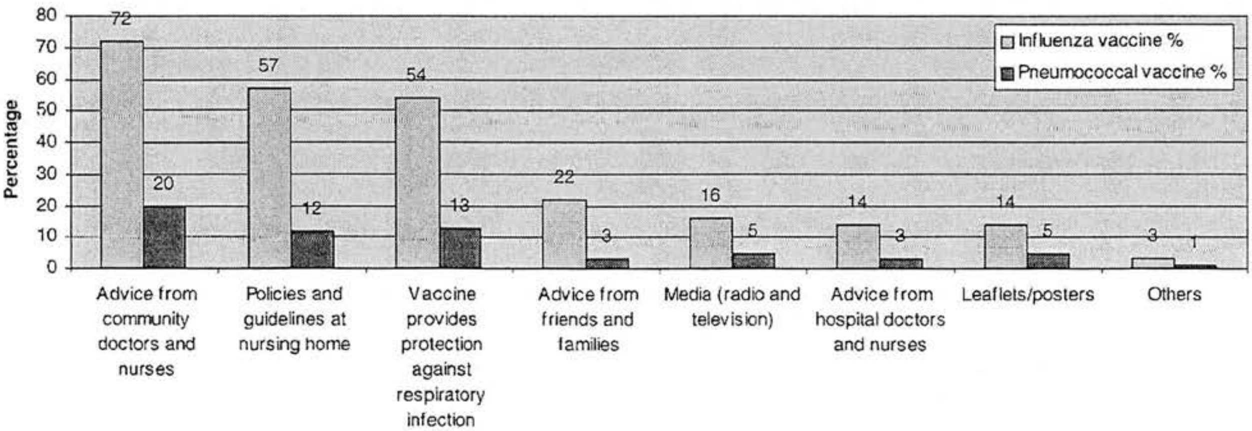


Fig. 3. Main reasons for receipt of influenza and pneumococcal vaccine.

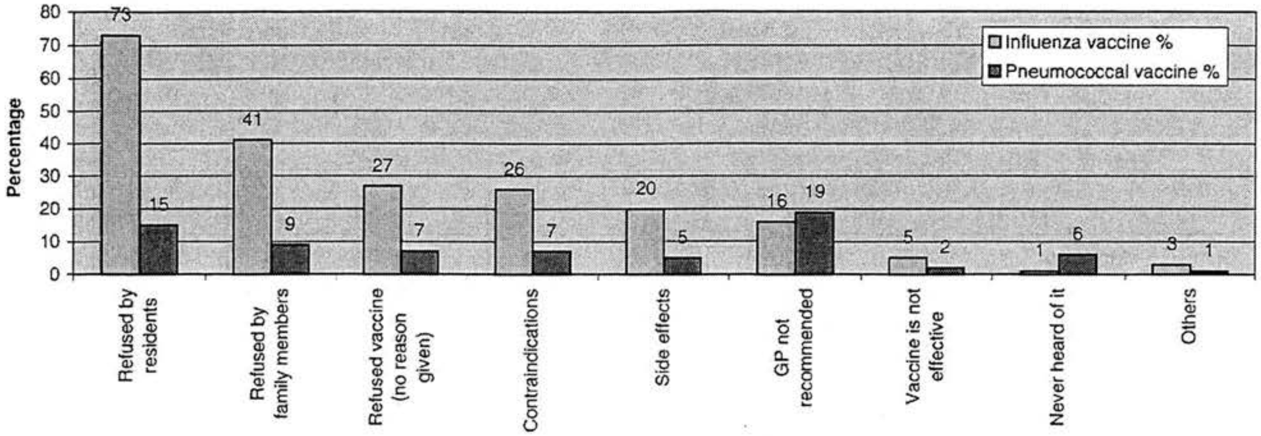


Fig. 4. Main reasons for non-receipt of influenza and pneumococcal vaccine.

vaccination was higher than pneumococcal vaccination: verbal agreement (27% versus 3%), written policies with set target (24% versus 5%) and written policies without set target (17% versus 2%) (Fig. 2). Over 70% of nursing homes did not provide information on pneumococcal vaccination policies.

7. Main reasons for receipt and non-receipt of vaccine

The most reported reasons for receipt of influenza vaccine were advice from community doctors and nurses (72%), nursing home policies and guidelines (57%) and efficacy against respiratory infection (54%) (Fig. 3). Similar reasons were indicated for receiving pneumococcal vaccine (20, 12 and 13%, respectively).

The most common reasons for non-receipt of influenza vaccine were refusal by residents (73%), and family members (41%) (Fig. 4). The predominant reasons for non-receipt of pneumococcal vaccine were that it was not recommended by their GPs (19%) and refusals by residents (15%).

8. Discussion

Overall, coverage of influenza and pneumococcal vaccine was 85 and 11%, respectively of residents in the present study. No differences in the average number of residents and the presence of immunization policies were documented between nursing homes that took part and did not take part in the survey. This suggests that our results appear to reflect all nursing homes throughout Scotland. Previous surveys in the UK [20] and US [21] showed an increased trend in coverage of influenza vaccine in the elderly over time. In the UK, coverage of influenza vaccine in the elderly nursing home residents was 45% in 1988–1989 [2], 67% in 1991–1992 [22], 77% in 1995 [23] and 89% in 1998–1999 [20]. The rate of influenza vaccination in the present study exceeded the target level of 65% among recommended groups in Scotland [24]. Nevertheless, about 8% of nursing homes failed to achieve 60–69% coverage of influenza vaccine. The observed high coverage of influenza vaccine is likely to be due to growing awareness of vaccination and changes in national vaccination recommendations and reimbursement policies by the UK Department of Health. Influenza vaccine coverage of above 80% can reduce the transmission of influenza virus in nursing homes by indirect protection (herd immunity) [5,25,26]. Therefore, nursing homes with high vaccine coverage are not only less likely to have outbreaks than those with low vaccine coverage but also more likely to reduce influenza morbidity and mortality. We found that 74% of nursing homes had optimal influenza vaccine coverage of between 80 and 100% of residents. Since the records of influenza and pneumococcal vaccinations were based on nursing home medical/nursing records rather than patient GP records, our results are likely to underestimate the coverage of these vaccines.

To our knowledge, this is the first national survey on coverage of pneumococcal vaccine in nursing home residents in the UK. Coverage of pneumococcal vaccine was very low (11%) in the present study. Pneumococcal vaccine coverage was higher in US nursing homes (38%) [27] and in Canadian long-term care facilities (71%) [28] in 1999. Although nursing homes have closed and high-risk populations, which provide ideal conditions for spread of pneumococci, outbreaks of pneumococcal disease have been rarely reported in UK nursing homes. The UK epidemiological studies have shown that the incidence of invasive pneumococcal disease in the elderly, aged 65 years and above, is 21–36 per 100,000 persons [29,30], but rates vary substantially in Europe and North America, ranging from 25 to 90 per 100,000 persons [31]. Case-fatality rates range from 18 to 40% [32–34]. Current 23-valent polysaccharide vaccine included stereotypes caused all reported outbreaks [7,35]. Studies indicate that outbreaks of pneumococcal disease are likely to occur in nursing homes with low vaccine coverage [3,6,36]. These data highlight the importance of pneumococcal vaccination in the elderly nursing home residents in the UK. Therefore, re-evaluation of current vaccination policies is needed in the UK.

Our data show that there was a substantial disparity in the coverage of influenza and pneumococcal vaccine. Previous studies in the US and UK indicate that low coverage of pneumococcal vaccine may reflect uncertainty of vaccine effectiveness, misconception about adverse reactions, lack of reimbursements and policies and unclear recommendations [37,38]. In Scotland, GP payment mechanisms similar to influenza vaccination are not yet in place for pneumococcal vaccine and may influence its administration to the elderly and other high-risk groups.

9. Reasons for receipt and non-receipt of vaccines

In common with previous surveys [3,39,40], we found that recommendations from community doctors and nurses were the principal reason for being vaccinated. However, in comparison with influenza vaccination, pneumococcal vaccination was more than three-fold less likely to be recommended. Surveys from the UK and US highlighted that between 73 and 91% of nursing homes provided pneumococcal vaccine based on physician discretion [3,40]. Polices for vaccination was reported to be an important factor for receiving influenza and pneumococcal vaccine. Similar to our previous study in general practices and hospital care settings [18,38], the presence of vaccination policies was reported to be an effective means for increasing pneumococcal vaccination rates in nursing homes. In keeping with other reports [3,41], nursing homes in Scotland are less likely to have policies on pneumococcal vaccination than influenza vaccination. We also found that the perceived efficacy of vaccine was an important reason for receipt of vaccines. Influenza vaccination behavior in high-risk patients also showed similar findings [39]. The predominant reason for not receiving influenza or pneumococcal vaccine was due to refusal of vaccine by residents or family members or no specific reason in the present study. Therefore, greater emphasis is needed in increasing awareness of risk of disease and the benefits of vaccination in nursing home residents and their family members.

10. Strategies for vaccination

The extension of pneumococcal vaccination policy to residents of long-term care facilities offers the opportunity to vaccinate at the time of annual influenza vaccination. This can undoubtedly enhance the use of pneumococcal vaccine in this at-risk group. In the US, a national objective has been set to achieve coverage of influenza and pneumococcal vaccine in over 90% for residents of long-term care facilities and other high-risk groups for the year 2010 [42]. There is no clear set target for pneumococcal vaccination in the UK. In the present study, only 6% of nursing homes had systematic vaccination records despite half of them expressing the view that these would improve vaccine coverage. Surveys have shown that the determination of pneumococcal vaccination status in individual long-term care residents is difficult and represents a major barrier for pneumococcal vaccination because of misconceptions about the risk of adverse reactions following revaccination [3,43]. The available evidence indicates that second dose of pneumococcal vaccine does not appear to be associated with serious adverse reactions [44,45]. Thus, pneumococcal vaccine could be given to patients with unknown vaccination history [10,46]. Studies in US nursing homes identified that vaccination was low priority among physicians [3,36]. Improved knowledge of adult vaccination in health care professionals may reduce missed opportunities for vaccination during consultations.

Difficulty in obtaining consent on behalf of incompetent residents was stated to be one of the important barriers to increased influenza and pneumococcal vaccination rates and this has been noted by others [47]. Data from Canada indicate that obtaining consent for vaccination on admission for current and future years is associated with higher influenza and pneumococcal vaccination rates [28]. Our findings also showed that vaccination programs organized by nursing staff were considered as an effective strategy for enhancing coverage of influenza and pneumococcal vaccine. It has been documented that organized vaccination programs are the most important strategy to improve influenza and pneumococcal vaccination rates [48]. Standing orders for nurses could allow for the easier administration of vaccines in long-term care facilities [49].

11. Conclusions

Our results highlight a large gap between influenza and pneumococcal vaccination rates in nursing homes. This is mainly due to lack of national recommendations and reimbursement policies for pneumococcal vaccination. Changes in attitudes, knowledge and practice of healthcare professionals and public together with the implementation of organized vaccine delivery strategies and systematic vaccination records are crucial in improving vaccination rates in nursing home residents and other long-term care facilities. Further studies in understanding of patients and clinicians vaccine preventable behaviors would aid in increasing coverage of these vaccines in high-risk patients.

Acknowledgements

The authors would like to thank the staff in nursing homes throughout Scotland for their cooperation in this survey. We are also grateful to the staff at the Scottish Centre for Infection and Environmental Health and the Information and Statistics Division in Scotland, in particular to Kenny McIntyre and Patricia Cassels, for their help in obtaining information and data entry.

References

[1] Muder RR. Pneumonia in residents of long-term care facilities: epidemiology, etiology, management and prevention. Am J Med 1998;105:319–30.

[2] Nicholson K, Baker D, Farquhar A, et al. Acute upper respiratory tract viral illness and influenza immunization in homes for the elderly. Epidemiol Infect 1990;105:609–18.

[3] Quick RE, Hoge CW, Hamilton DJ, Whitney C, Borges M, Kobayashi J. Underutilization of pneumococcal vaccine in nursing homes in Washington State: report of serotype-specific outbreak and a survey. Am J Med 1993;94:149–52.

[4] Monto A, Ohmit S, Margulies J, et al. Medical practice-based influenza surveillance: viral prevalence and assessment of morbidity. Am J Epidemiol 1995;141:502–6.

[5] Arden N, Monto A, Ohmit S. Vaccine use and the risk of outbreaks in a sample of nursing homes during an influenza epidemic. Am J Public Health 1995;85:399–401.

[6] Nuorti J, Butler J, Crutcher JM. Outbreak of multidrug-resistant pneumococcal pneumonia and bacteraemia among unvaccinated nursing home residents. N Engl J Med 1998;338:1861–8.

[7] Gleich S, Morad Y, Echague R, Miller JR, Kornblum J, Sampson JS, et al. *Streptococcus pneumoniae* serotype 4 outbreak in a home for the aged: report and review of recent outbreaks. Infect Control Hosp Epidemiol 2000;21:711–7.

[8] Butler JC, Cetron MS. Pneumococcal drug resistance: the new special enemy of old age. Clin Infect Dis 1999;28:730–5.

[9] Monto AS, Hornbuckle K, Ohmit SE. Influenza vaccine effectiveness among elderly nursing home residents: a cohort study. Am J Epidemiol 2001;154:155–60.

[10] MMWR. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997;46:1–24.

[11] Ohmit S, Arden N, Monto A. Effectiveness of inactivated influenza vaccine among nursing home residents during an influenza type A (H3N2) epidemic. J Am Geriatr Soc 1999;47:165–71.

[12] Shapiro ED, Berg AT, Austrian R, Schroeder D, Parcells V, Margolis A, Adair RK, Clemens JD. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med, 1991;325:1453–60.

[13] Butler J, Breiman R, Campbell J, Lipman H, Broome C, Facklam R. Pneumococcal polysaccharide vaccine efficacy: an evaluation of current recommendations. JAMA 1993;270:1826–31.

[14] Postma M, Baltussen R, Heijnen M, de Berg LT, Jager J. Pharmacoeconomic of influenza vaccination in the elderly: reviewing the available evidence. Drugs Ageing 2000;17:217–27.

[15] Nichol K, Baken L, Wuorenma J, Nelson A. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. Arch Intern Med 1999;159:2437–42.

[16] Ament A, Baltussen R, Duru G, et al. The cost effectiveness of pneumococcal vaccination for older people: a study in five western European countries. Clin Infect Dis 2000;31:444–50.

[17] McDonald P, Friedman E, Banks A, Anderson R, Carman V. Pneumococcal vaccine campaign based in general practices. BMJ 1997;314:1094–8.

[18] Kyaw MH, Wayne B, Chalmers J, Jones IG, Campbell H. Influenza and pneumococcal vaccine distribution and use in primary care and hospital settings in Scotland: coverage, practice and policies. Epidemiol Infect, in press.

[19] Department of Health. Immunisation against infectious disease London: HMSO, 1996.

[20] Gupta A, Morris G, Thomas P, Hasan M. Influenza vaccination coverage in old people's home in Camarthenshire, UK, during the winter of 1998/99. Vaccine 2000;18:2471–5.

[21] MMWR. Influenza and pneumococcal vaccination levels among persons aged ≥65 years—United States. MMWR 2001;50:532–7.

[22] Evans M, Wilkinson E. How complete is influenza vaccination coverage? A study in 75 nursing and residential home for the elderly people. Br J Clin Pract 1995;45:419–21.

[23] Evans M. Monitoring influenza immunisation uptake in nursing homes. Commun Dis Rep 1996;6:R170–2.

[24] Chief Medical Officer (CMO). Influenza immunisation. Scottish Executive. Health Department, 2001.

[25] Patriarca P, Weber J, Parker R. Risk factors for outbreaks of influenza in nursing homes: a case control study. Am J Epidemiol 1986;124:114–9.

[26] Gross P, Rodstein M, LaMontagne J. Epidemiology of acute respiratory illness during an influenza outbreak in a nursing home. Arch Intern Med 1988;148:559–61.

[27] Buikema A, Singleton J, Sneller V et al. Influenza and pneumococcal vaccination in nursing homes, US, 1995–1999, In: Abstracts from the 35th National Immunization Conference. Atlanta, Georgia, 2001 [Abstract].

[28] Stevenson CG, McArthur MA, Naus M, Abraham E, McGeer AJ. Prevention of influenza and pneumococcal pneumonia in Canadian long-term care facilities: how are we doing? CMAJ 2001;164:1413–9.

[29] Sleeman K, Knox K, George R. Invasive pneumcoccal disease in England and Wales: vaccination implications. J Infect Dis 2001;183:239–46.

[30] Kyaw MH, Clarke S, Jones IG, et al. Incidence of invasive pneumococcal disease in Scotland. Epidemiol Infect, in press.

[31] Butler JC, Schuchat A. Epidemiology of pneumococcal infections in the elderly. Drugs Aging 1999;15:11–9.

[32] Breiman R, Spika J, Navarro V, Darden PM, Darby CP. Pneumococcal bacteremia in Charleston County, South Carolina a decade later. Arch Intern Med 1990;150:1401–5.

[33] Plouffe JF, Breiman RF, Facklam RR. Bacteraemia with *Streptococcus pneumoniae*: implications for therapy and prevention. JAMA 1996;275:194–8.

[34] Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs) Report. Emerging Infections Program Network *Streptococcus pneumoniae*, 2000 (preliminary). Available at: http:www.cdc.gov/ncidod/dbmd/abcs. Accessed 10 November 2001.

[35] Sheppard D, Bartlett K, Lampiris H. *Streptococcus pneumoniae* transmission in chronic-care facilities: description of an outbreak and review of management strategies. Infect Control Hosp Epidemiol 1998;19:851–3.

[36] MMWR. Outbreaks of pneumococcal pneumonia among unvaccinated residents in chronic care facilities—Massachusetts, October 1995, Oklahoma, February 1996, and Maryland, May–June 1996. MMWR 1997;46:60–62.

[37] Fedson DS. Pneumococcal vaccination in the United States and 20 other developed countries, 1981–1996. Clin Infect Dis 1998;26:1117–23.

[38] Kyaw MH, Bramley JC, Chalmers J, Jones IG, Campbell H. Pneumococcal vaccination: opinion of general practitioners and hospital doctors in Scotland, 1999–2000. Commun Dis Public Health 2001;4:42–8.

[39] Nichol K, Lofgren R, Gapinski J. Influenza vaccination: knowledge, attitudes and behaviour among high-risk outpatients. Arch Intern Med 1992;152:106–10.

[40] Kyaw MH, Nguyen-Van-Tam J, Pearson J. Family doctor advice is the main determinant of pneumococcal vaccine uptake. J Epidemiol Community Health 1999;53:589–90.

[41] Nichol KL, Grimm MB, Peterson DC. Immunizations in long-term care facilities: policies and practice. J Am Geriatr Soc 1996;44:349–55.

[42] US Department of Health and Human Services. In: Proceedings of Conference on Healthy people 2010 (in two volumes). Washington, DC: US Department of Health and Human Services, 2000.

[43] MMWR. Outbreak of pneumococcal pneumonia among unvaccinated residents of a nursing home—New Jersey, April 2001. MMWR 2001;50:707–9.

[44] Fine MJ, Smith MA, Carson CA, et al. Efficacy of pneumococcal vaccination in adults: a meta-analysis of randomized controlled trails. Arch Intern Med 1994;154:2666–77.

[45] Jackson LA, Benson P, Sneller V-P, Butler JC, Thompson RS, Chen RT, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. JAMA 1999;281:243–8.

[46] Whitney CG, Schaffner W, Butler JC. Rethinking recommendations for use of pneumococcal vaccines in adults. Clin Infect Dis 2001;33:662–75.

[47] Russell ML. Influenza vaccination in Alberta long-term care facilities. CMAJ 2001;164:1423–7.

[48] Nichol KL. Ten-year durability and success of an organised program to increase influenza and pneumococcal vaccination rates among high-risk adults. Am J Med 1998;105:385–92.

[49] MMWR. Adult immunization programs in national strategies: quality standards and guidance for program evaluation and use of standing orders programs to increase adult vaccination rates. MMWR 2000;49:1–28.

Epidemiol. Infect. (2002), **128**, 445–455. © 2002 Cambridge University Press
DOI: 10.1017/S0950268802006891 Printed in the United Kingdom

Influenza and pneumococcal vaccine distribution and use in primary care and hospital settings in Scotland: coverage, practice and policies

M. H. KYAW[1,3]*, B. WAYNE[3], J. CHALMERS[2], I. G. JONES[3] AND H. CAMPBELL[1]

[1] *University of Edinburgh, Department of Public Health Sciences, Edinburgh*
[2] *Information and Statistics Division of the Common Services Agency, Edinburgh*
[3] *Scottish Centre for Infection and Environmental Health, Clifton House, Clifton Place, Glasgow G3 7LN*

(*Accepted 9 January 2002*)

SUMMARY

A survey of the coverage, distribution and the factors associated with use of influenza and pneumococcal vaccines among general practitioners (GPs) in primary care and in hospital settings was carried out in 53 general practices in Scotland taking part in the 'Continuous Morbidity Recording' (CMR) programme. The annual vaccine distribution increased substantially among 53 general practices from 1993 to 1999 and in Scotland as a whole from 1984 to 1999. From the questionnaire, overall coverage was 43% (95% CI 38–48) for influenza vaccine in the 2000–1 season and 13% (95% CI 9–16) for pneumococcal vaccine in the last 5 year period, in high-risk patients recommended for these vaccines by the Department of Health (DoH). Influenza vaccine coverage was highest in the elderly (65 years of age and above) at 62% (95% CI 59–74). Although pneumococcal vaccination is not currently recommended for all elderly, coverage of this vaccine was also higher in this group (22%, 95% CI 16–29). In the majority of patients (influenza vaccine, 98% and pneumococcal vaccine, 94%), vaccination was carried out in general practice. Only 2% of patients had received pneumococcal vaccination in a hospital setting. The level of influenza and pneumococcal vaccination varied with the level of deprivation. Most GPs considered that the responsibility for influenza and pneumococcal vaccination lay with them. Forty-five percent of GPs reported having a written policy with set target for influenza vaccination and 11% for pneumococcal vaccination.

INTRODUCTION

Influenza and pneumococci are important causes of hospitalization and deaths in the United Kingdom [1]. Influenza and pneumococcal vaccination reduces hospitalization and death in the elderly and persons with chronic medical conditions [2–4]. Influenza vaccine is effective in preventing at least 50% of severe respiratory illnesses, hospitalizations and deaths in the elderly and those living in long stay facilities [4, 5]. The current 23-valent pneumococcal polysaccharide vaccine covers over 88% of serotypes which cause disease in the United Kingdom [6, 7] and is reported to be 50–80% effective against invasive pneumococcal disease [8]. Both vaccines are currently recommended for persons at increased risk of influenza and pneumococcal disease and may be administered simultaneously at different sites [9]. Annual vaccination is required for influenza vaccine but not for pneumococcal vaccine which lasts for 5–10 years.

Information on the actual use of these vaccines in primary care and hospital settings is poor but limited evidence suggests that influenza vaccine and pneumococcal vaccines are underused in the United Kingdom. Estimated coverage for influenza vaccine has been reported to be 20–45% and 4–15% for pneumococcal vaccine among at-risk patients [10–12]. Only 0·5% of immunizations for influenza or pneumococcal vaccine

* Author for correspondence: Clifton House, Clifton Place, Glasgow G3 7LN.

were given in hospital settings [11, 13]. No studies have compared their distribution patterns, use and coverage among high-risk individuals in the primary care and hospital settings. We therefore report on the distribution of influenza and pneumococcal vaccines in 53 general practices in Scotland. We also examine views on vaccine indications, policies and responsibilities for vaccination among GPs and use of influenza and pneumococcal vaccines in primary care and hospital care. Since the CMR practices record diagnostic codes, it is possible to identify all patients meeting high-risk criteria and therefore be able to measure vaccination rates in these groups.

Data from this study should aid in the development of appropriate vaccination strategies and policies for improving coverage of influenza and pneumococcal vaccines among at-risk patients.

METHODS

The practice data were collected from 53 general practices which contribute to the 'Continuous Morbidity Recording' (CMR) system (which include more than 5% of the population of Scotland). Information obtained from CMR system is considered to be representative of the Scottish population in terms of sex, age, deprivation and rural/urban mix and geographic locations [14] and became part of the national 'core data set' on 1 April 1998. The CMR system requires at least one diagnosis to be recorded at each face-to-face contact between a GP and patient. The diagnoses are Read coded and all data are internally linked to build up a continuous record for each patient. The number of high-risk patients registered in the CMR practices was determined by searching for the specific diagnosis codes for chronic medical conditions. Data on the number of high-risk patients were based on persons rather than GP consultations, to ensure that patients who had more than one high-risk condition for influenza or pneumococcal vaccine were not counted more than once.

Information on the number of doses of influenza and pneumococcal vaccines distributed obtained from prescribing returns from the Primary Care Unit, Information and Statistics Division (ISD), NHS in Scotland. Data were examined for the whole of Scotland during 1984–99 and for the CMR practices during 1993–9. Based on the total number of high-risk patients and the total number of influenza and pneumococcal vaccine doses distributed in the CMR practices, we estimated the likely overall coverage of this vaccine in all high-risk patients and in patients who are recommended for vaccination by the Department of Health (DoH).

Using computer generated random selection, ten high-risk patients were selected from each of the 53 CMR practices. As the CMR system is completely anonymous, we do not know the names of the patients, but we supplied other details (date of birth, sex and postcode) of these patients which allowed GPs to identify them and their medical records. A questionnaire was sent to each GP asking them to review the medical records to identify whether these individuals had been vaccinated with influenza and/or pneumococcal vaccines in either a primary care or hospital setting. In addition, information on their views on vaccine indications, policies and responsibilities for vaccination programme was also requested. Each GP was offered a set fee for establishing and recording the vaccination status of their patients, to compensate for their time taken to review the (10) records and to answer the questionnaire.

We were able to check data on coverage of pneumococcal vaccine based on vaccine distribution statistics. We then made an estimate of total numbers of high-risk patients or required immunizations for influenza and pneumococci in Scotland based on the total numbers of high-risk patients registered in the CMR practices. We used the Carstairs Deprivation Scores [15] to determine whether deprivation status of the patient's area of residence was associated with the coverage of these vaccines. This measurement is based on postcode sector which is assigned a deprivation category, ranging from 1 to 7, 1 being the most affluent and 7 being the most deprived.

The annual number of influenza vaccine doses prescribed was calculated as the number of doses dispensed per 1000 population [16]. Pneumococcal vaccine use is presented as the number of doses dispensed per 10000 population as in the previous report [17]. Data analyses were carried out using SPSS version 10. χ^2 test for trend was used to determine the association between vaccine coverage and deprivation index. 95% confidence intervals and χ^2 tests for trends were calculated for vaccine coverage using the CIA programme (Gardner SB, Winter PD, Gardner MJ: London 1991).

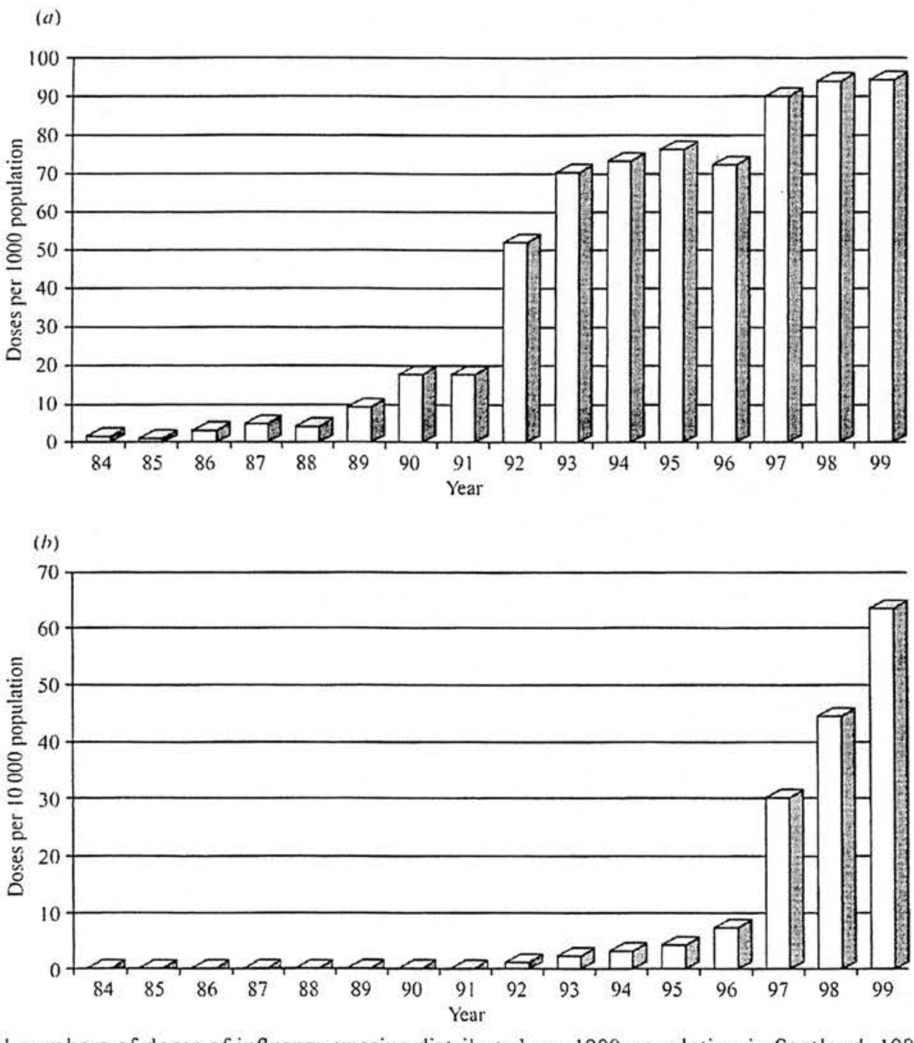
RESULTS

A substantial increase in the annual distribution of both influenza and pneumococcal vaccines occurred

Table 1. *Number of influenza and pneumococcal vaccine dispensed in the 53 CMR* practices, 1993–9*

	Influenza vaccine		Pneumococcal vaccine	
Year	No. of dose dispensed	Dose distributed per 1000 population	No. of dose dispensed	Dose distributed per 10000 population
1993	22180	72·2	58	1·9
1994	22618	73·6	237	7·7
1995	26813	87·3	768	25·0
1996	24955	81·2	196	6·4
1997	32624	106·2	1000	32·6
1998	33151	107·9	2092	68·1
1999	34106	111·0	1538	50·1

* An estimated population 307215 in 53 CMR practices.



ig. 1. (*a*) Annual numbers of doses of influenza vaccine distributed per 1000 population in Scotland, 1984–99. (*b*) Annual umbers of pneumococcal vaccine distibuted per 10000 population in Scotland, 1984–99.

ver the period 1984–99 in Scotland and in 1993–9 in e CMR practices (Fig. 1, Table 1). Of the 53 uestionnaires sent out to GPs within the CMR practices, 45 (84·9%) were returned and completed. The selected patients fell into eight categories; chronic pulmonary, heart, liver, renal disease, or diabetic

Table 2. (*a*) *Influenza vaccine coverage*, (*b*) *pneumococcal vaccine coverage* (*1999–2000*), *in high-risk patients*

High-risk conditions	No	Yes	Total	Coverage in all ages	(95% CI)	Coverage in < 64 years of age	Coverage in ≥ 65 years of age
(*a*) Influenza vaccine coverage in high-risk patients, 1999–2000							
Chronic pulmonary disease*	156	83	239	34·7	(29–41)	22·2	69·8
Chronic heart disease*	51	59	110	53·6	(44–63)	36·1	60·8
Chronic liver disease	3	4	7	57·1	(18–90)	25	100
Chronic renal disease*	2	4	6	66·7	(22–96)	60	100
Diabetic mellitus*	24	43	67	64·2	(52–76)	53·1	74·3
Asplenic disorders*	5	1	6	16·7	(0–64)	0	16·7
Elderly (65 years of age and above)	54	108	162	66·7	(59–74)		
Elderly (75 years of age and above)*	31	51	82	62·2	(51–73)		
Overall coverage for conditions indicated by the DoH	232	174	406	42·9	(38–48)		
Overall coverage for all high-risk conditions	235	178	413	43·1	(38–48)		
(*b*) Pneumococcal vaccine coverage in high-risk patients							
Chronic pulmonary disease†	216	23	239	9·6	(6–14)	4	25·4
Canonic heart disease†	93	17	110	15·5	(9–22)	8·3	18·9
Chronic liver disease†	6	1	7	14·3	(0·4–58)	0	33·3
Chronic renal disease†	6	0	6	0	(0–41)	0	0
Diabetic mellitus†	53	14	67	20·9	(12–33)	15·6	25·7
Asplenic disorders†	6	1	7	14·3	(0·4–58)	20	16·7
Elderly (65 years of age and above)	126	36	162	22·2	(16–29)		
Elderly (75 years of age and above)	64	18	82	21·9	(14–33)		
Overall coverage for conditions indicated by the DoH	362	52	414	12·6	(9–16)		
Overall coverage for all high-risk conditions	362	52	414	12·6	(9–16)		

CI, confidence interval, * recommend by the DoH (all elderly 65 years of age and above include for vaccination from September 2000, current policy also includes immunosuppressed patients, those living in nursing homes and long-term care facilities).

† recommend by the DoH (current vaccine policy also includes patients with immunodeficiency or immunosuppression).

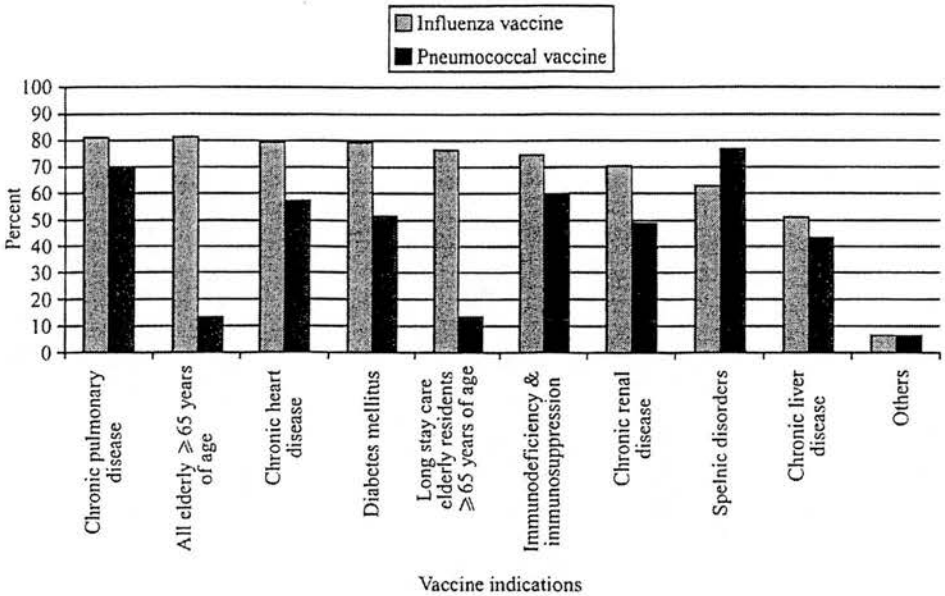


Fig. 2. Views on agreement of influenza and pneumococcal vaccine indications.

mellitus, asplenic disorders, the elderly (65 years of age and above) and the elderly (75 years of age and above) (Table 2).

Influenza vaccine

Distribution and coverage of vaccine among high-risk patients

Between 1984 and 1999, influenza vaccine distribution increased from 2 to 94 doses per 1000 population in Scotland, a 47-fold increase (Fig. 1a). The vaccine distribution substantially increased after 1991–2 and 1996–7. This improvement appears to be correlated with the official Department of Health (DoH) recommendations issued in 1992 and 1996. The distribution of influenza vaccine also increased in the CMR practices, from 72·2 to 111 per 1000 population, a 1·5 fold increase over the period 1993–9 (Table 1). Using patient-based data from the questionnaire, the overall coverage of influenza vaccine was 43% among high-risk patients recommended by the DoH. Coverage of influenza vaccine differed significantly in each category of patients, with higher coverage in the elderly and patients with chronic renal disease (67%) and lower coverage in patients with asplenic disorders (17%) and chronic pulmonary disease (35%) compared with other high-risk conditions (Table 2a).

Views on vaccine indications

Most GPs agreed that influenza vaccination should be targeted to the elderly and patients with chronic medical conditions. Nevertheless, patients with asplenic disorders and chronic liver disease were less likely to be considered as indications for influenza vaccination than other conditions (Fig. 2).

Vaccination policies

Figure 3 shows influenza vaccination policies among GPs. Forty-five percent of GPs indicated that they had written a policy with set target. Only 4 % of GPs reported that they did not have any form of influenza vaccination policy.

Vaccination responsibility

GPs views on the primary responsibility for influenza vaccination are presented in Figure 4. Fifty-three percent of GPs thought that the primary responsibility for influenza vaccination should lie with GPs and 40% thought it should lie with the patient.

Pneumococcal vaccine

Distribution and coverage of vaccine among high-risk patients

There was no pneumococcal vaccine distribution until 1991. Annual distribution rates for pneumococcal vaccine increased from 0 to 63 doses per 10000 population during the period 1991–9 for the whole of Scotland (Fig. 1b). The vaccine distribution was very low, 1–7 doses per 10000 population during the period 1992–6. A substantial growth occurred after

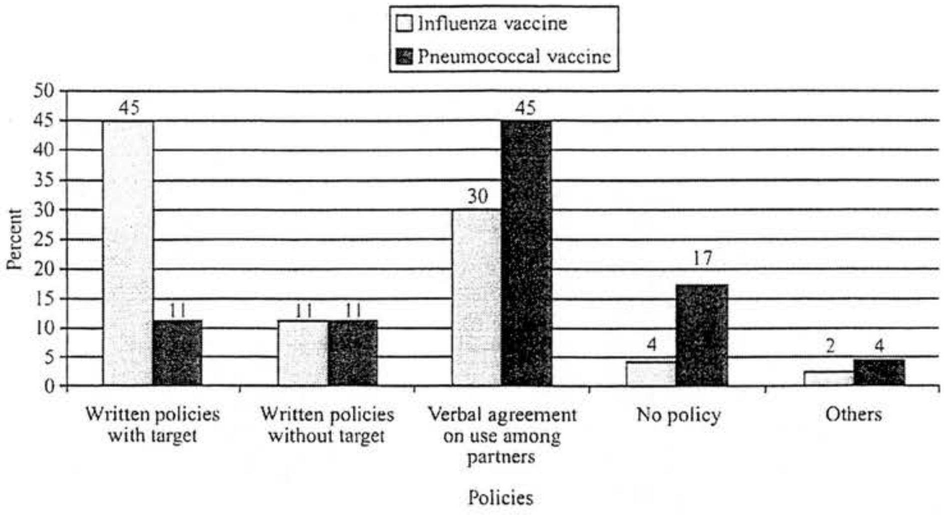


Fig. 3. Influenza and pneumococcal vaccination policies in primary care.

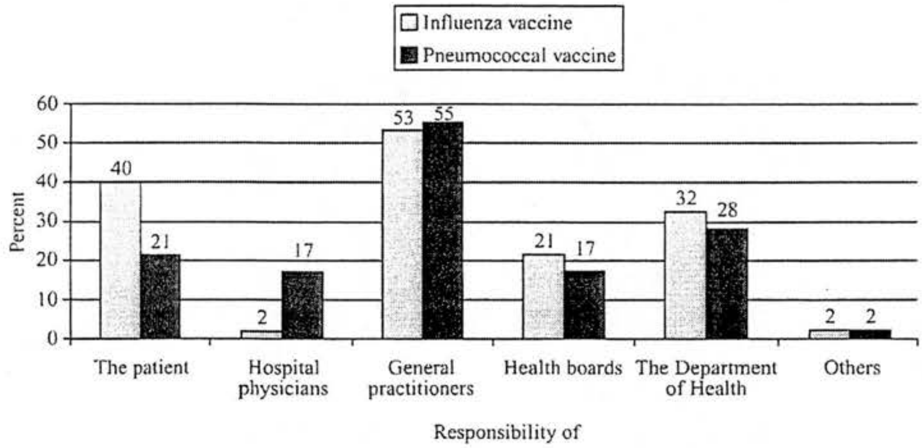


Fig. 4. Views on primary responsibility of influenza and pneumococcal vaccination.

1996, from 30 doses per 10000 population in 1997 to 63 doses per 10000 population in 1999. The improvement of vaccine distribution coincided with the DoH recommendations for pneumococcal vaccination in at-risk patients, issued in 1996. In the CMR practices, the levels of pneumococcal vaccine distribution rose from 1·9 doses to 50·1–68·1 doses per 10000 population during the period 1993–1998/9, a 26–36 fold increase (Table 1). The overall coverage of pneumococcal vaccine in the last 5 year period was 13% among patients who met DoH indications for the vaccine from the questionnaire survey. Coverage of pneumococcal vaccine was 0–22% among patients in the eight risk categories, with lower coverage in patients with chronic renal disease (0%) and chronic pulmonary disease (10%) and the higher level coverage in the elderly (22%) (Table 2b).

Views on vaccine indications

Figure 2 indicates views on pneumococcal vaccine indications among GPs. Patients with asplenic conditions (76%), and chronic pulmonary disease (70%) were more likely to be considered as indications for pneumococcal vaccination than other conditions. Only 13% of GPs felt that pneumococcal vaccination was indicated for all elderly (including those living in long-term care facilities).

Vaccination policies

Pneumococcal vaccination policies among GPs are shown in Figure 3. Eleven percent of GPs reported that they had a pneumococcal vaccination policy with or without a set target. A majority of GPs (45%)

Table 3. *Number of patients indicated for influenza and pneumococcal vaccine and the estimated influenza and pneumococcal vaccine coverage in the CMR practices and the whole of Scotland, 1993–9*

High-risk conditions	No. of patients*
(*a*) Estimated number of high-risk patients in the CMR practices	
Chronic liver disease	265
Chronic pulmonary disease	13696
Chronic renal disease	318
Diabetes	3991
Chronic heart disease	6684
Immunosuppression/immunodeficiency	41
Asplenia	125
Elderly 65 years of age and above†	45495
Elderly 75 years of age and above	20150
(*b*) Estimated vaccine coverage based on the number of high-risk patients registered in the CMR practices and vaccine prescription data	
Pneumococcal vaccine coverage, 1993–9	
Conditions recommend by the DoH	23·4% (5889/25120)
All conditions (including all elderly)	8·3% (5889/70615)
Influenza vaccine coverage, 1999–2000	
Conditions recommend by the DoH (including the elderly aged 75 years and above but not include those 65 years of age and above)	75·8% (34106/45005)
All conditions (including all elderly)	48·5% (34106/70350)
(*c*) Estimated number of required influenza and pneumococcal vaccinations in Scotland	
Estimated number of high-risk patients (= Number of required influenza and pneumococcal vaccinations)	Influenza vaccine (rate per 1000 population)
All high-risk conditions	
418646	81
1202787 (including the elderly aged 65 years and above)	234·9
760948 (including the elderly aged 75 years and above)	148·6
Without chronic liver disease	
414229	80
1198370 (including the elderly aged 65 years and above)	234
756531 (including the elderly aged 75 years and above)	147·7

* Patients are based on person (patients with two high-risk conditions = 1374, three high-risk conditions = 78 and four high-risk conditions = 2).

DoH recommendations for pneumococcal vaccination include all listed high-risk conditions except the elderly.

DoH recommendations for influenza vaccine is recommended for all listed high-risk conditions (except chronic liver diseases), with persons with living in long-term care facilities († vaccination extend to all the elderly 65 years and above since September 2000).

reported that they had verbal agreement on its use among partners.

Vaccination responsibility

Figure 4 shows GPs' views on the primary responsibility for pneumococcal vaccination. Most GPs (55%) believed that the responsibility for pneumococcal vaccination should be taken by GPs. The responsibility of vaccination was not related to use of vaccine (105/255 (41%) *vs*. 73/158 (46%), $P = 0{\cdot}368$) for influenza vaccine) and (28/263 (11%) *vs*. 24/151 (16%), $P = 0{\cdot}126$ for pneumococcal vaccine).

Table 4. *Level of influenza and pneumococcal vaccine coverage relation to socioeconomic statuses*

Deprivation* category	No (%)	Yes (%)	Total
Influenza vaccine			
1	10 (4·4)	9 (5·1)	19
2	26 (11·6)	24 (13·7)	50
3	56 (24·9)	55 (31·4)	111
4	86 (38·2)	59 (33·7)	145
5	14 (6·2)	12 (6·9)	26
6	26 (11·6)	14 (8)	40
7	7 (3·1)	2 (1·1)	9
$P = 0{\cdot}2293$ (χ^2 for trend $= 1{\cdot}445$)	225 (100)	175 (100)	400
Pneumococcal vaccine			
1	15 (4·3)	4 (8)	19
2	43 (12·3)	7 (14)	50
3	90 (25·6)	22 (44)	112
4	132 (37·6)	13 (26)	145
5	24 (6·8)	2 (4)	26
6	38 (10·8)	2 (4)	40
7	9 (2·6)	– (0)	9
$P = 0{\cdot}0109$ (χ^2 for trend $= 6{\cdot}483$)	351 (100)	50 (100)	401

* 1 being the most affluent and 7 being the most deprived.

Estimated number of high-risk patients, vaccine coverage based on vaccine prescription data in the CMR practices, the total required immunisations

A total estimated number of high-risk patients and the elderly population in the 53 CMR practices are given in Table 3*a*. The estimated influenza vaccine coverage in 2000–1 season and the estimate cumulative pneumococcal vaccine coverage in 1993–9 based on vaccine prescription data in the CMR practices show in Table 3*b*. The estimated number of people (with and without the elderly) recommended for vaccination and the projected total number of required immunizations for influenza and pneumococcal vaccines are displayed in Table 3*c*.

Place of vaccination

Most patients were vaccinated in general practice: accounting for 98·9% of influenza vaccine coverage and 94·2% of pneumococcal vaccine coverage. Very few patients had received these vaccines at home: 1·1% of influenza vaccine coverage and 3·8% of pneumococcal vaccine coverage. Only 2% of patients who received pneumococcal vaccine, were vaccinated in hospital care setting.

Socioeconomic status in relation to vaccine coverage

The level of influenza and pneumococcal vaccination varied with the level of deprivation (Table 4). However, the association between deprivation index and vaccination was noted for pneumococcal vaccine ($P = 0{\cdot}0109$, χ^2 for trend $= 6{\cdot}483$) only, not influenza vaccine ($P = 0{\cdot}23$, χ^2 for trend $= 1{\cdot}45$).

DISCUSSION

We found that patient-based data from the questionnaire, an estimated 43% and 13% of at-risk patients defined by the DoH guidelines received influenza vaccine in 2000–1 season and pneumococcal vaccine in the last 5 year period respectively. Since the CMR practices were selected to represent a fair cross-section of Scottish general practices and as there is no evidence to suggest GPs in the CMR practices may have different influenza and pneumococcal immunization characteristics compared to other GPs, our results should be reasonably representative of the whole of Scotland. Data on coverage of primary immunization coverage at 2 years old were the same in the CMR practices as in Scotland as a whole. Although influenza and pneumococcal vaccines coverage remains less than optimal, the annual vaccine distribution has increased substantially in the CMR practices and in Scotland as a whole in the last 3 years.

Vaccine distribution

Data on distribution of influenza [16, 18] and pneumococcal vaccine [17] in other developed countries have shown a similar pattern of increased vaccine distribution in recent years. We found that the increase in influenza and pneumococcal vaccine distribution appeared to be related to vaccination recommendations in 1992 and 1996. Reports on influenza [18] and pneumococcal [17] vaccination policies in Europe and North America also suggest that the presence of recommendations is strongly correlated with the levels of influenza and pneumococcal vaccine use and distribution. For patients recommended for vaccination by the DoH advice, there was over one and a half fold difference in coverage of pneumococcal vaccine, between the data from the survey and an estimated figure based on the total number of vaccines distributed in the CMR practices. These data suggest that not all total number of vaccines actually dispensed were used in current target groups. Our estimate shows that the number of required influenza vaccinations per 1000 population is 81 if persons with chronic medical conditions are considered. This rises to 234·9 if all the elderly, 65 years of age and above are also included. The latter rate is substantially higher than that reported from a previous study in Wales (148 per 1000 population) [19] and the influenza vaccine distribution rate from prescription data in Scotland.

Influenza vaccine coverage

Influenza vaccine coverage in the present survey was similar to previous United Kingdom studies, which reported vaccine coverage of 17–41% in patients with underlying medical conditions [13, 20] and 43–48% in the elderly [12, 20]. Coverage of influenza vaccine (also pneumococcal vaccine) was particularly low in patients with chronic pulmonary disease and asplenic conditions among the vaccine recommended groups and those aged < 64 years compared with $\geqslant 65$ years of age. This might have been influenced by the small number of patients included in each of the high-risk categories and the higher number of patients with chronic pulmonary disease in age group < 64 years. It is likely that the elderly ($\geqslant 65$ years) may have a higher number of GP visits than those $\leqslant 64$ years of age, leading to 4–6 fold higher influenza and pneumococcal vaccine coverage. Although the levels of influenza vaccine coverage have increased in the elderly, coverage of the vaccine remains suboptimal for other high-risk conditions. It has been recommended that to achieve herd immunity particularly in nursing homes, influenza coverage should exceed 80% [21]. Recently, the United Kingdom has adopted influenza vaccination policy for all elderly 65 years of age and above with fees payable to GPs [22]. This may encourage influenza vaccine use among GPs and could achieve high vaccination coverage in the future. Vaccination has shown to be associated with cost saving of $75 per elderly per year [23]. Thus vaccination is the most effective intervention to reduce the impact of influenza in at-risk groups.

Pneumococcal vaccine coverage

As in the surveys from England [10, 11], the overall coverage of pneumococcal vaccine in the last 5 year period appears low at 13% among recommended patients. This is very similar to influenza vaccine coverage in the late 1980s. Although target groups for influenza and pneumococcal vaccines overlap considerably, there was a remarkable difference in coverage of influenza and pneumococcal vaccine in the present survey. This indicates that many opportunities have been missed for pneumococcal vaccination during annual influenza vaccination. Many studies have reported that the incidence and case-fatality rates of pneumococcal disease are substantially higher in the elderly and high-risk groups [24, 25]. In addition, drug resistant pneumococci are increasing in the United Kingdom [26, 27]. Nevertheless, we found that over 70% of high-risk patients had not received pneumococcal vaccine. Studies have reported that low coverage of pneumococcal vaccine may be due to lack of advice from GPs [11, 28, 29]. This may be due to uncertainty regarding the benefits of pneumococcal vaccination, inadequate knowledge of risk and the impact of pneumococcal disease [30]. It appears that these factors are likely to influence the use of vaccine among GPs. Although the current United Kingdom policy does not advise GPs to vaccinate all elderly aged 65 years, vaccination coverage in this group is high relative to other high-risk conditions.

Vaccination strategies

In the present survey, GPs were more likely to target influenza vaccination than pneumococcal vaccination to at-risk patients, particularly the elderly. This may explain the lower levels of pneumococcal vaccine coverage in the elderly and other at-risk groups compared with influenza vaccine coverage. It appears that the protective benefits of pneumococcal vaccination have been largely unrecognized by GPs. Our data also suggest the need for education of adult vaccine preventable diseases in medical training. Variations of influenza and pneumococcal vaccination policies among GPs and disparities in coverage of both vaccines among various high-risk groups emphasize the need for improved guidelines and policies by the DoH. We also found that receipt of pneumococcal vaccine varied with level of deprivation in the area of residence. Therefore, improved strategies to increase vaccine-seeking behaviours are required to increase the coverage of these vaccines in all segments of population. Since lack of awareness on vaccine and the risk of disease are the principal reasons for not receiving the vaccines, particularly pneumococcal vaccine [28, 31–33], education of health care workers (doctors, nurses and pharmacists) and patients, improved practice guidelines, and effective methods to identify high-risk patients such as letter/postcard/chart/computer reminder would help to enhance coverage of these vaccines [29]. Since coverage of both vaccines was lower in those aged < 64 years compared with $\geqslant 65$ years, attention should be paid to vaccinate the non-elderly with chronic medical conditions. A study from England has demonstrated that an organized public campaign of pneumococcal vaccination can increase coverage of vaccine, from 4·5% to 19·5% among at-risk patients and use of vaccine among GPs, from 17% to 89% [10]. The majority of patients accept influenza or pneumococcal vaccine when offered by a health care workers [29]. This emphasizes the critical role of heath care workers in increasing coverage of influenza and pneumococcal vaccines.

Although most GPs considered that the responsibility for influenza and pneumococcal vaccinations should lie with them, coverage of these vaccines remained inadequate. Vaccine cost may partially be responsible for low pneumococcal vaccine coverage among high-risk groups. At present, there are no payment mechanisms for pneumococcal vaccination in Scotland. The extent to which financial incentives and disincentives impact on adult vaccination coverage should be evaluated to assess to what extent improved vaccine coverage could be achieved with reimbursement policies. In addition, understanding of the factors involved in the reasons for receipt and non-receipt of pneumococcal vaccine among at-risk patients could be helpful in informing vaccination strategies. Given the current coverage of influenza and pneumococcal vaccine, primary care based influenza and pneumococcal vaccination alone may not be feasible to achieve optimal vaccine coverage among high-risk persons. Evidence from the United Kingdom and United States suggests that a majority of high-risk patients had a previous hospitalization in the last 5 years [34]. Therefore, hospital-based influenza and pneumococcal vaccination programmes have the potential to be an effective strategy to deliver the vaccines to those who have greatest need of them. In the present study, only 2% of patients had received pneumococcal vaccination in the hospital care setting, suggesting that very little effort has been made to improve coverage of these vaccines by health care workers in hospitals. In addition, most GPs did not have a written policy with a set target especially for pneumococcal vaccination. It appears that a clear vaccination policy and financial support for vaccination are necessary to achieve a higher coverage of influenza and pneumococcal vaccine among high-risk individuals [35].

In conclusion, although coverage of influenza and pneumococcal vaccines was suboptimal, the number of these vaccines distributed and reported coverage in general practice in the recent years has improved substantially. Since influenza and pneumococcal vaccination has been reported to be effective, improved coverage of these vaccines among at-risk patients can yield significant public health benefits. A clear vaccination policy, organized education and national campaign of influenza and pneumococcal vaccination could improve coverage of these vaccines. Clinicians in both general practice and hospital settings should ensure that their patients are aware of the risk of influenza and pneumococcal disease and benefit for both vaccines.

ACKNOWLEDGEMENTS

We would like to thank the staff, in particular to Patricia Cassels, Mark Getty, Matthew Armstrong, Bill Gold, James McNally, Ann Mochrie and Jean Goldie at the Scottish Centre for Infection and Environmental Health, the Information and Statistics Division and Scottish Executive. The Chief Scientist Office of the Scottish Executive Health Department funded this research.

REFERENCES

1. Nguyen-Van-Tam J, Neal KR. Clinical effectiveness, policies, and practices for influenza and pneumococcal vaccines. Seminar Resp Infect 1999; **14**: 184–95.
2. MMWR. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997; **46**: 1–24.
3. Nichol KL. The addictive benefits of influenza and pneumococcal vaccinations during influenza seasons among elderly persons with chronic lung disease. Vaccine 1999; **17**: S91–3.
4. MMWR. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2000; **49** (RR03): 1–38.
5. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons: a meta-analysis and review of the literature. Ann Intern Med 1995; **123**: 518–27.
6. Kyaw MH, Clarke S, Edwards G, Jones IG, Campbell H. Serotypes/groups distribution and antimicrobial

resistance of invasive pneumococcal isolates: implication for vaccine strategies. Epidemiol Infect 2000; **125**: 561–72.

7. Sleeman K, Knox K, George R, et al. Invasive pneumococcal disease in England and Wales: vaccination implications. J Infect Dis 2001; **183**: 239–46.
8. Fedson DS. The clinical effectiveness of pneumococcal vaccination: a brief review. Vaccine 1999; **17**: S85–90.
9. Department of Health. Immunisation against infectious disease London: HMSO, 1996.
10. McDonald P, Friedman E, Banks A, Anderson R, Carman V. Pneumococcal vaccine campaign based in general practices. BMJ 1997; **314**: 1094–8.
11. Kyaw MH, Nguyen-Van-Tam J, Pearson J. Family doctor advice is the main determinant of pneumococcal vaccine uptake. J Epidemiol Commun Hlth 1999; **53**: 589–90.
12. Irish C, Alli M, Gilham C, Joseph C, Watson J. Influenza vaccine uptake and distribution in England and Wales, July 1989–June 1997. Health Trends 1998; **30**: 51–5.
13. Nguyen-Van-Tam J, Nicholson K. Influenza immunization; vaccine offer, request and uptake in high-risk patients during the 1991/2 season. Epidemiol Infect 1993; **111**: 347–55.
14. Information and Statistics Division (ISD). Scottish Health Statistics 1998. UK (Edinburgh): ISD, 1999.
15. Registrar General Office (RGO). 1991 annual report: Registrar General Office (RGO), 1992.
16. Fedson DS, Hannoun C, Leese J, et al. Influenza vaccination in 18 developed countries, 1980–1992. Vaccine 1995; **13**: 623–7.
17. Fedson DS. Pneumococcal vaccination in the United States and 20 other developed countries, 1981–1996. Clin Infect Dis 1998; **26**: 1117–23.
18. Fedson DS, Hirota Y, Shin H, et al. Influenza vaccination in 22 developed countries: an update to 1995. Vaccine 1997; **15**: 1506–11.
19. Watkins J, Rogers C, Evans J. Implications of age-based policies for influenza immunisation. Lancet 1999; **353**: 208–9.
20. Gupta A, Makinde K, Morris G, Thomas P, Hasan M. Influenza immunization coverage in older hospitalised patients during winter 1998–99 in Carmarthenshire, UK. Age Ageing 2000; **29**: 211–3.
21. Patriarca P, Weber J, Parker R, et al. Risk factors for outbreaks of influenza in nursing homes: a case control study. Am J Epidemiol 1986; **124**: 114–9.
22. Chief Medical Officer (CMO). Major changes to the policy on influenza immunisation. CMO's update, 2000; **26**: 1.
23. Nichol K, Margolis K, Wuorenma J, Strenberg TV. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. NEJM 1994; **331**: 778–84.
24. Butler JC, Schuchat A. Epidemiology of pneumococcal infections in the elderly. Drugs Aging 1999; **15**: 11–9.
25. Fedson D, Musher D, Eskola J. Pneumococcal vaccine. In: Plotkin SA, Orenstein WA, eds. Vaccines. Philadelphia: W. B. Saunder Company, 1999: 553–607.
26. Reacher MH, Shah A, Livermore DM, et al. Bacteraemia and antibiotic resistance of its pathogens reported in England and Wales between 1990 and 1998: trend analysis. BMJ 2000; **320**: 213–6.
27. Kyaw MH, Clarke S, Jones IG, Campbell H. Incidence of invasive pneumococcal disease in Scotland, 1988–1999. Epidemiol Infect 2002; **128**: 139–48.
28. MMWR. Reasons reported by Medicare beneficiaries for not receiving influenza and pneumococcal vaccinations – United States. MMWR 1999; **48**: 886–90.
29. MMWR. Adult immunization programs in national strategies: Quality standards and guidance for program evaluation and use of standing orders programs to increase adult vaccination rates. MMWR 2000; **49**: 1–28.
30. Fedson D. Adult immunization. Summary of the National Vaccine Advisory Committee Report. JAMA 1994; **272**: 1133–7.
31. Nicholson KG. Immunisation against influenza among people aged over 65 living at home in Leicestershire during winter 1991–2. BMJ 1993; **306**: 974–6.
32. Siriwardena A. Targeting pneumococcal vaccination to high-risk groups: a feasibility study in one general practice. Postgrad Med J 1999; **75**: 208–12.
33. Findlay PF, Gibbons Y, Primrose W, Ellis G, Downie G. Influenza and pneumococcal vaccination: patient perceptions. Postgrad Med J 2000; **76**: 215–7.
34. Fedson DS, Houck P, Bratzler D. Hospital-based influenza and pneumococcal vaccination: Sutton's Law applied to prevention. Infect Control Hosp Epidemiol 2000; **21**: 692–9.
35. Kyaw MH, Bramley JC, Chalmers J, Jones IG, Campbell H. Pneumococcal vaccination: opinion of general practitioners and hospital doctors in Scotland, 1999–2000. Commun Dis Publ Hlth 2001; **4**: 42–8.

SHORT REPORT

A survey of vaccine coverage and antibiotic prophylaxis in splenectomised patients in Scotland

M H Kyaw, E M Holmes, J Chalmers, I G Jones, H Campbell

J Clin Pathol 2002;55:472–474

Aims: To determine the coverage of vaccine and antibiotic prophylaxis in splenectomised patients in Scotland.
Methods: Patients who had undergone splenectomy between 1 January 1988 and 31 December 1998 were identified. A questionnaire was sent to general practitioners to validate vaccine and antibiotic status for these patients.
Results: A total of 974 living splenectomised patients were identified during the study period. Information on vaccine and antibiotic status was available for 708 (73%) and 770 (79%) of living patients, respectively. Coverage of pneumococcal vaccine (88%) was higher than that of *Haemophilus influenza* type b (Hib) conjugate vaccine (70%) or meningococcal vaccine (51%). Only 47% of patients received all three vaccines. A higher coverage was also documented for pneumococcal vaccine (28%) than Hib (19%) and meningococcal vaccine (14%) before elective splenectomy. Only 13% received all three vaccines before splenectomy. Coverage of influenza vaccine increased significantly, from 76% in the 1997/1998 season to 96% in the 2000/2001 season. Antibiotic prophylaxis was received by 67% of all patients. The current recommendation, comprising pneumococcal and Hib vaccination and antibiotic prophylaxis, was received by only 52% of the patients. There was no association between the coverage of vaccine and socioeconomic status.
Conclusion: Further improvement in coverage of recommended vaccines and antibiotic prophylaxis is still needed to reduce the risk of serious infection in this high risk group.

Patients without spleens are at a significantly increased risk of serious infection with encapsulated bacteria, especially *Streptococcus pneumoniae, Haemophilus influenzae* type b (Hib), and *Neisseria meningitidis*.[1] Antibiotics and polysaccharide pneumococcal, meningococcal, influenza, and Hib conjugate vaccines are available for the prevention of postsplenectomy infection and are recommended for all splenectomised patients by the Department of Health (DoH) and the British Committee for Standards in Haematology (BCSH), with the exception of meningococcal polysaccharide vaccine.[2,3] Because the adherence to preventive measures has been reported to be low,[4,5] we conducted this study to determine the coverage of appropriate vaccination and antibiotic prophylaxis in splenectomised patients in Scotland during an 11 year period from 1988 to 1998.

"Patients without spleens are at a significantly increased risk of serious infection with encapsulated bacteria"

METHODS

Patients who underwent splenectomy from 1 January 1988 to 31 December 1998 were identified using the Scottish Morbidity Record (SMR01), which is collected at discharge from all episodes of hospital inpatient or day case care. It records information on demography, number of hospital admissions, and the clinical nature of the patient treatment episode. SMR01 records were linked to General Register Office (Scotland) death registrations using probability matching to exclude patients who had died because their medical records would not be available to general practitioners. A questionnaire was sent to general practitioners of living patients requesting details of elective or emergency splenectomy, antibiotic prescribing, and vaccination with pneumococcal, meningococcal, Hib, and influenza vaccines. A reminder was sent to those who did not respond after six weeks. The Carstairs deprivation score[6] was used to determine the deprivation index values of the patients' areas of residence and the coverage of these vaccines. Data analysis was performed on SPSS version 10 and Stata (Stata Corporation, version 6, 1999; College Station, Texas, USA) for Fisher's exact test.

RESULTS

There were 974 living patients who had undergone splenectomy during the study period. Information on vaccination status was available for 708 (73%) of those patients. A higher coverage was documented for pneumococcal vaccine (622 of 708, 88%) and Hib vaccine (468 of 664, 70%) than for meningococcal vaccine (317 of 619, 51%) (table 1). All three vaccines were received by 47% (269 of 576) of the patients. Vaccination status before elective splenectomy was recorded for 541 (56%) of the patients. Coverage of pneumococcal vaccine (153 of 541, 28%) was higher than that of Hib (83 of 435, 19%) or meningococcal vaccine (48 of 335, 14%) for elective splenectomy. All three vaccines were received by 13% (38 of 291) of the patients. An increasing trend in coverage of influenza vaccine was noted between 1997 and 2000: from 76% in the 1997/1998 season to 96% in the 2000/2001 season. Of the 770 (79%) patients in whom antibiotic status was recorded, 518 (67%) received antibiotic prophylaxis. Coverage was 35% (201 of 571) for all three vaccines and antibiotic prophylaxis and 52% (333 of 634) for pneumococcal and Hib vaccines and antibiotic prophylaxis.

There were no significant trends in the deprivation index values for coverage of vaccine with ($p = 0.12$) or without ($p = 0.14$) antibiotic prophylaxis for the combination of pneumococcal and Hib vaccine. Similar findings were recorded for the combination of pneumococcal, meningococcal, and Hib vaccine with ($p = 0.07$) or without ($p = 0.08$) antibiotic prophylaxis. In addition, no association was documented for influenza vaccine coverage and the value of the deprivation index (Fisher's exact test, $p = 0.46$).

Abbreviations: BCSH, British Committee for Standards in Haematology; DoH, Department of Health; Hib, *Haemophilus influenza* type b; SMR, Scottish Morbidity Record

Table 1 Vaccine and antibiotic coverage in splenectomised patients

DoH and BCSH recommendations	Vaccine or antibiotic prophylaxis	Timing of vaccination	Vaccine coverage N	%
Yes	Pneumococcal	All cases (before or after surgery)	622/708	88
		Two weeks before elective surgery	153/541	28
Yes	Hib	All cases (before or after surgery)	468/664	70
		Two weeks before elective surgery	83/435	19
No	Meningococcal	All cases (before or after surgery)	317/619	51
		Two weeks before elective operation	48/335	14
Yes	Influenza	All cases (before or after surgery)		
		Season 1997–8	16/21	76
		Season 1998–9	24/27	89
		Season 1999–2000	82/89	92
		Season 2000–2001	329/342	96
Yes	Antibiotic prophylaxis	–	518/770	67
Yes	Pneumococcal and Hib	All cases (before or after surgery)	439/641	68
		Two weeks before elective surgery	80/406	20
No	Pneumococcal and meningococcal	All cases (before or after surgery)	305/602	51
		Two weeks before elective surgery	44/313	14
No	Hib and meningococcal	All cases (before or after surgery)	276/588	47
		Two weeks before elective surgery	40/305	13
No	Pneumococcal, meningococcal and Hib	All cases (before or after surgery)	269/576	47
		Two weeks before elective surgery	38/291	13
Yes	Pneumococcal and Hib vaccine and antibiotic prophylaxis	All cases (before or after surgery) for vaccines and after surgery for antibiotic prophylaxis	333/634	52
No	Pneumococcal, meningococcal, and Hib vaccine and antibiotic prophylaxis	All cases (before or after surgery) for vaccines and after surgery for antibiotic prophylaxis	201/571	35

BCSH, British Committee for Standards in Haematology; DoH, Department of Health; Hib, *Haemophilus influenza* type b.

DISCUSSION

Optimal management comprising pneumococcal and Hib vaccines and antibiotic prophylaxis was received by 52% of the patients. Annual influenza vaccination uptake increased substantially during 1997 and 2000 and reached over 96% coverage in the 2000/2001 season. A review of studies of postsplenectomy infection between 1952 and 1987, before the availability of Hib conjugate vaccine, found that most cases of postsplenectomy infection are caused by *S pneumoniae* (57% of cases), followed by *H influenzae* (6%), *N meningitidis* (4%), and *Escherichia coli* (4%), with a 32–77% case fatality rate.[1] The widespread use of Hib conjugate vaccine appears to influence the prevalence of causative organisms of postsplenectomy infection. Passive surveillance data in the UK, based on 77 cases of postsplenectomy infection between 1994 and 1998, showed that *S pneumoniae* and *N meningitidis* accounted for 87% and 3% of cases, respectively.[7] The remaining 10% of cases were caused by *Listeria monocytogenes*, *E coli*, *Klebsiella* sp, *Salmonella typhimurium*, and others.

The coverage of vaccine was higher in this large survey compared with previous UK studies, which reported 35.5% in 1986–90 for pneumococcal vaccine[4] and 10% in 1992–96 for Hib and meningococcal vaccines.[5] A recent study in England showed that the coverage of pneumococcal, meningococcal, and Hib vaccine was 79%, 51%, and 40%, respectively.[8] However, in our present study, it is possible that vaccine coverage was lower among splenectomy patients who had died, and that our results are biased.

In Scotland, the guidelines for the management of postsplenectomy infection are based on the DoH and BCSH recommendations. As with other vaccinations and preventive measures, general practitioners are responsible for ensuring that these patients receive appropriate preventive measures. However, there is a need for a national splenectomy register to identify those patients who have not received vaccines or antibiotic prophylaxis in Scotland. This could also be used to generate a regular reminder to general practitioners regarding their patients' prophylaxis status. Our data also suggest that most general practitioners and other clinicians follow recommendations for pneumococcal and influenza vaccines but not for other vaccines. Although the administration of bacterial vaccines is recommended for at least two weeks before elective splenectomy,[2,3] compliance with this schedule was suboptimal. It appears that compliance with current recommendations for the timing of vaccination with regard to splenectomy was poor among clinicians. Although the effectiveness of pneumococcal, meningococcal, and Hib vaccines in asplenic patients is uncertain, the increased susceptibility to serious infection and the documented safety and potential benefits of these vaccines justify their use in these patients. As yet, meningococcal polysaccharide vaccine is not included in the general recommendations, the vaccine is likely to offer benefits to these patients and thus should be considered.

New conjugate vaccines may offer better protection against these organisms. Meningococcal group C conjugate vaccine has recently been recommended for routine immunisation in

Take home messages

- Coverage of pneumococcal vaccine (88%) was higher than that of *Haemophilus influenza* type b (Hib) conjugate vaccine (70%) or meningococcal vaccine (51%) and only 47% of patients received all three vaccines
- A higher coverage was also documented for pneumococcal vaccine (28%) than Hib (19%) and meningococcal vaccine (14%) before elective splenectomy and only 13% of patients received all three vaccines before splenectomy
- Coverage of influenza vaccine increased from 76% in the 1997/1998 season to 96% in the 2000/2001 season
- Antibiotic prophylaxis was received by 67% of all patients and only 52% of patients received pneumococcal and Hib vaccination and antibiotic prophylaxis (the current recommendation)
- Thus, it is apparent that further improvement in coverage of recommended vaccines and antibiotic prophylaxis is still needed to reduce the risk of serious infection in this high risk group

asplenic patients.[9] The decision to use pneumococcal conjugate vaccine is expected soon. Although our study found no significant correlation between the coverage of the combination of pneumococcal polysaccharide and Hib vaccine or the combination of pneumococcal, meningococcal, and Hib vaccine, with or without antibiotic prophylaxis, studies in the USA have highlighted low socioeconomic status in relation to poor coverage of childhood[10] and adult vaccines.[11]

"As yet, meningococcal polysaccharide vaccine is not included in the general recommendations, the vaccine is likely to offer benefits to these patients and thus should be considered"

Although current guidelines recommend life long antibiotic use in these patients,[3] only 67% of patients in our study had received antibiotic prophylaxis. We do not know how many of these patients had discontinued the prophylactic regimen or were taking macrolides (those allergic to penicillin). The rapid emergence of drug resistant pneumococcus complicates this preventive measure and highlights the need for the improved use of pneumococcal polysaccharide vaccine, which covers most drug resistant serotypes. Our survey indicates a high degree of coverage for pneumococcal and influenza vaccine but suboptimal coverage for Hib and meningococcal vaccine and antibiotic prophylaxis despite the existence of national guidelines and the risk of serious infection in these patients. Efforts to increase the coverage of recommended vaccines and antibiotic prophylaxis should continue.

ACKNOWLEDGEMENTS

We would like to thank general practitioners, the staff at the Information and Statistics Division, Practitioner Services, Scottish Centre for Infection and Environmental Health, in particular J Mair, K Pearson, B Wayne, and P Cassels, for their help and assistance with the data for this study. The Chief Scientific Office of the Scottish Executive Health Department funded this research.

....

Authors' affiliations

M H Kyaw, H Campbell, Public Health Sciences, University of Edinburgh, Teviot Place, Edinburgh EH 8 9AG, UK
E M Holmes, I G Jones, Scottish Centre for Infection and Environmental Health, Clifton House, Clifton Place, Glasgow G3 7LN, UK
J Chalmers, Information and Statistics Division of the Common Services Agency, Trinity Park House, South Trinity Road, Edinburgh EH5 3SQ, UK

Correspondence to: Dr M H Kyaw, Scottish Centre for Infection and Environmental Health, Clifton House, Clifton Place, Glasgow G3 7LN, UK; Moe.Kyaw@scieh.csa.scot.nhs.uk

Accepted for publication 19 December 2001

REFERENCES

1 **Holdsworth R**, Irving A, Cuschieri A. Post-splenectomy sepsis and its mortality rate: actual versus perceived risk. *Br J Surg* 1991;**78**:1031–8.
2 **Department of Health.** *Immunisation against infectious disease.* London: HMSO, 1996.
3 **Working Party of the British Committee for Standards in Clinical Haematology Task Force.** Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *BMJ* 1996;**312**:430–4.
4 **Kinnersley P**, Wilkinson C, Srinivasan J. Pneumococcal vaccination after splenectomy: survey of hospital and primary care records. *BMJ* 1993;**307**:1398–9.
5 **Waghorn DJ**, Mayon-White R. A study of 42 episodes of overwhelming post-splenectomy infection: is current guidance for asplenic individuals being followed? *J Infect* 1997;**35**:289–94.
6 **Registrar General Scotland**. *1991 annual report: Registrar General Office (RGO)*. Edinburgh: General Register Office for Scotland, 1992.
7 **Waghorn DJ**. Overwhelming infection in asplenic patients: current best practice preventive measures are not being followed. *J Clin Pathol* 2001;**54**:214–18.
8 **Cummins A**, Millership S. Local review of the provision of prophylaxis and advice to patients without functioning spleens. *Commun Dis Public Health* 2001;**4**:144–5.
9 **Chief Medical Officer**. *Current vaccine and immunisation. Meningococcal immunisation for asplenic patients*. 9th March 2001. London: Department of Health (http:www.doh.gov.uk/cmo/cmoh.htm).
10 **Robinson CA**, Sepe SJ, Lin KF. The president's child immunisation initiative: a summary of the problem and the response. *Public Health Rep* 1993;**108**:419–25.
11 **Morbidity and Mortality Weekly Report (MMWR)**. Reasons reported by Medicare beneficiaries for not receiving influenza and pneumococcal vaccinations—United States. *MMWR Morb Mortal Wkly Rep* 1999;**48**:886–90.

Journal of Clinical Microbiology, May 2002, p. 1834–1837 Vol. 40, No. 5
0095-1137/02/$04.00+0 DOI: 10.1128/JCM.40.5.1834–1837.2002

Invasive Meningococcal Disease in Scotland, 1994 to 1999, with Emphasis on Group B Meningococcal Disease

Moe H. Kyaw,[1,2]* Stuart C. Clarke,[3] Peter Christie,[2] Ian G. Jones,[2] and Harry Campbell[1]

Public Health Sciences, University of Edinburgh, Edinburgh,[1] and Scottish Centre for Infection and Environmental Health[2] and Scottish Meningococcus and Pneumococcus Reference Laboratory,[3] Glasgow, United Kingdom

Received 6 September 2001/Returned for modification 9 December 2001/Accepted 3 February 2002

A review was carried out on 774 invasive meningococcal isolates reported to the active meningococcal surveillance system in Scotland from 1994 to 1999. This showed that serogroups B (51.7%) and C (39.2%) caused the majority of disease. The six common PorB proteins (4, 1, 15, 2B, 12, and 21) and PorA proteins (serosubtypes) (P1.4, P1.15, P1.9, P1.14, P1.7, and P1.16) accounted for 50 and 51% of all group B isolates, respectively, during the study period.

Neisseria meningitidis is the most common cause of bacterial meningitis in the United Kingdom and throughout the world (27). The organism has at least 13 serogroups, 20 serotypes, 10 serosubtypes, and 13 immunotypes (19, 25). Of the five different structural classes of outer membrane proteins (OMPs), class 2 or 3 OMP (PorB) is expressed by all meningococci and defines the serotype (14). Class 1 protein (PorA) is generally present in most meningococci and determines the serosubtype (2).

Worldwide, serogroups A, B, C, Y, and W135 are the most common causes of disease (19), and their distributions differ with age, time, and geographic location (23, 25). Although polysaccharide and conjugate meningococcal vaccines are available for the prevention of serogroup A, C, Y, and W135 disease, there is no effective vaccine against group B meningococcal disease. Since group B polysaccharide is poorly immunogenic and has cross-reactivity with human neonatal neural tissue (13), a vaccine against group B disease has been developed based on OMPs. These vaccines have been shown to be safe and immunogenic in infants (8, 17) and adults (18). Studies have suggested that OMP vaccines need to include multiple OMPs due to the diversity of the prevalence of OMPs in group B strains. Therefore, the identification of the important OMPs associated with group B isolates would aid in selecting appropriate OMPs for vaccine formulation. We herein examine the characteristics of invasive meningococcal isolates and identify the distribution of group B serotypes and serosubtypes reported to the population-based surveillance system in Scotland from 1994 to 1999.

The estimated population under surveillance was 5.1 million in the study period. A case of invasive meningococcal disease (IMD) was defined when *N. meningitidis* was isolated from a normally sterile site such as blood, cerebrospinal fluid, or joint fluid. Serogrouping was performed for all invasive isolates. Latex agglutination and coagglutination tests were used for the serogrouping of *N. meningitidis* (7, 12). Serotyping and serosubtyping were carried out by a whole-cell enzyme-linked immunosorbent assay (1, 14). The full set of meningococcal monoclonal antibodies available from the National Institute of Biological Standards and Control (http://www.nibsc.ac.uk) was used for the immunotyping of the disease strains. The set is the same as that used by the other major meningococcal reference laboratories, including the Meningococcal Reference Unit at Manchester Public Health Laboratory, Manchester, United

TABLE 1. Annual cases of meningococcal disease by age group and serogroup in Scotland, 1994 to 1999

Age group	No. of cases by serogroup in indicated yr																				
	1994			1995			1996			1997			1998			1999			1994 to 1999		
	B	C	Others	B	C	Others	B	C	Others	B	C	Others	B	C	Others	B	C	Others	B	C	Others
<1 yr	19	4	0	15	2	5	22	3	5	20	2	2	23	6	1	21	3	1	120	20	14
1 yr	14	7	0	8	2	2	7	1	1	4	5	2	11	3	1	7	8	1	51	26	7
2 to 4 yr	15	5	0	12	3	3	13	4	3	8	7	5	4	6	0	14	9	0	66	34	11
5 to 17 yr	9	8	1	12	13	3	15	11	4	11	14	3	9	36	3	14	24	0	70	106	14
18 to 34 yr	2	1	0	7	3	3	9	11	4	14	15	1	5	10	2	14	25	1	51	65	11
35 to 49 yr	4	1	0	0	2	2	1	6	0	1	5	1	2	3	2	2	4	1	10	21	6
50 to 64 yr	4	0	0	4	4	0	3	2	0	1	2	1	0	3	0	7	2	0	19	13	1
≥65 yr	1	2	0	2	1	0	3	3	1	0	2	2	0	5	2	7	5	2	13	18	7
All ages	68	28	1	60	30	18	73	41	18	59	52	17	54	72	11	86	80	6	400	303	71

* Corresponding author. Mailing address: Scottish Centre for Infection and Environmental Health, Clifton House, Clifton Place, Glasgow, G3 7LN, United Kingdom. Phone: 0141-300-1184. Fax: 0141-300-1170. E-mail: Moe.Kyaw@scieh.csa.scot.nhs.uk.

Kingdom. Data analysis was performed with SPSS version 10 (SPSS INc., Chicago, Ill.).

There were 774 cases of IMD in all: 400 cases (51.7%) were caused by group B strains, 303 cases (39.2%) by group C strains, 11 cases (1.4%) by group Y strains, 7 cases (0.9%) by group W135 strains, 7 cases (0.9%) by other strains (including those of groups Y, Z, 29E, and X), and 46 cases (5.9%) by nongroupable strains. The proportion of cases of IMD due to group C strains increased significantly from 1994 to 1999, but the incidence of group B disease was relatively stable (Table 1). The majority of cases of IMD occurred in patients aged 5 to 17 years and <1 year. There was also an increase in the number of cases of IMD in patients aged 5 to 17 and 18 to 34 years during the study period.

Cases of IMD caused by group B strains were more prevalent in patients aged <1 year (30%), while those caused by group C strains were more prevalent in patients aged 5 to 17 years (35%) and 18 to 34 years (21%). The incidence of both group B IMD and group C IMD was highest in patients aged <1 and 1 year (33.3 and 14.5 cases per 10,000 persons for group B disease and 5.6 and 7.4 cases per 10,000 persons for group C disease, respectively).

The distribution of group B meningococcal serotypes and subtypes was substantially diverse and varied annually (Tables 2 and 3). Of the 212 isolates (53%) with serotype information, serotypes 4, 1, 15, 2B, 14, and 21 (in descending order of prevalence) accounted for 50% of the total isolates from 1994 to 1999. The predominant serotype was 4. The six most prev-

TABLE 2. Annual distribution of PorB group B meningococci, 1994 to 1999

Yr	Serotype	No. of cases	%
1994	4	15	22.1
	15	12	17.6
	2B	11	16.2
	1	5	7.4
	21	4	5.9
	14	3	4.4
	2A	1	1.5
	4,15	1	1.5
	4,21	1	1.5
	TY[a]	53	77.9
	NT[b]	15	22.1
	All[c]	68	100
1995	4	10	16.7
	15	9	15
	1	3	5
	2B	3	5
	21	2	3.3
	14	1	1.7
	TY	28	46.7
	NT	32	53.3
	All	60	100
1996	4	19	26
	1	4	5.5
	14	3	4.1
	22	3	4.1
	2B	3	4.1
	2A	2	2.7
	15	2	2.7
	TY	36	49.3
	NT	37	50.7
	All	73	100
1997	4	17	28.8
	1	7	11.9
	15	3	5.1
	2B	1	1.7
	14	1	1.7
	21	1	1.7
	4,21	1	1.7
	TY	31	52.5
	NT	28	47.5
	All	59	100
1998	4	14	25.9
	1	7	14
	15	4	7.4
	2A	1	1.9
	2B	1	1.9
	21	1	1.9
	TY	28	51.9
	NT	26	48.1
	All	54	100
1999	4	18	20.9
	1	10	11.6
	14	2	2.3
	15	2	2.3
	2A	1	1.2
	2B	1	1.2
	21	1	1.2
	4,21	1	1.2
			1.2
	TY	36	41.9
	NT	50	58.1
	All	86	100
1994 to 1999	4	93	23.3
	1	36	9
	15	32	8
	2B	20	5
	14	10	2.5
	21	9	2.3
	2A	5	1.3
	22	3	0.8
	4,21	3	0.8
	4,15	1	0.3
	TY	212	53
	NT	188	47
	All	400	100

[a] TY, total serotypeable isolates.
[b] NT, nontypeable isolates.
[c] All serotypeable and nonserotypeable isolates.

TABLE 3. Annual distribution of PorA group B meningococci, 1994 to 1999

Yr	Serosubtype	No. of cases	%	Yr	Serosubtype	No. of cases	%
1994	P1.7	11	16.2		P1.3	1	1.7
	P1.4	10	14.7		P1.10	1	1.7
	P1.10	8	11.8		P1.12	1	1.7
	P1.15	6	8.8		P1.19	1	1.7
	P1.14	4	5.9				
	P1.16	4	5.9		TY	34	57.6
	P1.2	3	4.4		NT	25	42.4
	P1.9	3	4.4		All	59	100
	P1.1,7	2	2.9				
	P1.2,5	2	2.9				
				1998	P1.4	13	24.1
	TY[a]	53	77.9		P1.9	5	9.3
	NT[b]	15	22.1		P1.15	5	9.3
	All[c]	68	100		P1.16	4	7.4
					P1.5	3	5.6
					P1.14	3	5.6
1995	P1.4	10	16.6		P1.1	1	1.9
	P1.16	7	11.7		P1.3	1	1.9
	P1.9	6	10				
	P1.15	5	8.3		TY	35	64.8
	P1.7	5	8.3		NT	19	35.2
	P1.10	3	5		All	54	100
	P1.2	3	5				
	P1.14	2	3.3				
	P1.3	1	1.7	1999	P1.4	12	14
	P1.6	1	1.7		P1.9	9	10.5
	P1.13	1	1.7		P1.15	9	10.5
					P1.14	8	9.3
	TY	44	73.3		P1.3	4	4.7
	NT	16	26.7		P1.5	3	3.5
	All	60	100		P1.12	1	1.2
					P1.13	1	1.2
					P1.16	1	1.2
1996	P1.4	19	26		P1.7,16	1	1.2
	P1.15	7	9.6				
	P1.14	4	5.5		TY	49	57
	P1.9	3	4.1		NT	37	43
	P1.10	3	4.1		All	86	100
	P1.3	2	2.7				
	P1.16	2	2.7				
	P1.2,5	2	2.7	1994 to 1999	P1.4	72	18
	P1.12	1	1.4		P1.15	38	9.5
	P1.13	1	1.4		P1.9	28	7
	P1.5	1	1.4		P1.14	25	6.3
	P1.6	1	1.4		P1.7	20	5
					P1.16	20	5
	TY	46	63		P1.10	15	3.8
	NT	27	37		P1.5	11	2.8
	All	73	100		P1.2	11	2.8
					P1.3	9	2.3
					P1.1,7	3	0.7
1997	P1.4	8	13.6		P1.13	3	0.7
	P1.15	6	10.2		P1.12	3	0.7
	P1.5	4	6.8		P1.6	2	0.5
	P1.14	4	6.8		P1.19	1	0.3
	P1.7	3	5.1				
	P1.9	2	3.4		TY	261	65.3
	P1.16	2	3.4		NT	139	34.7
	P1.2	1	1.7		All	400	100

[a] TY, total serotypeable isolates.
[b] NT, nonserotypeable isolates.
[c] All serotypeable and nonserotypeable isolates.

alent serosubtypes expressed by group B were P1.4, P1.15, P1.9, P1.14, P1.7, and P1.16, accounting for 51% of all isolates (Table 3). The predominant serosubtype was P1.4.

Although a shift in the age distribution of group B disease has been detected recently in older children and adults in the United States (20) and Canada (11), we did not observe this in the present study. The incidence of both group B and C disease in infants in Scotland was significantly higher than that in the

United States (20). In many countries, an increase in the prevalence of group B meningococcal disease was reported to parallel the high prevalence of serotype 4 (3), which was associated with the majority of disease in New Zealand from 1991 to 1999 (86% of cases) (16), in Canada from 1987 to 1995 (4, 15), in Spain from 1987 to 1992 (53% of cases) (5), and in other European countries from 1992 to 1995 or 1996 (10). In the United States (13, 14), serotypes 15, 14, 10, 1, and 2a accounted for 67% of all serotypeable isolates between 1992 and 1998 (24). A multivalent PorB vaccine composed of the six most common serotypes in Scotland accounted for 40 to 74% of all serosubtypes (86 to 100% of serotypeable isolates) in the study period.

Studies show that an increased incidence of group B disease has been associated with hypervirulent strains (9, 21). In developed countries, group B was associated with P1.4 in The Netherlands (22) and New Zealand (16) and with P1.7,16 in Norway (26). Surveillance of meningococcal disease in Europe showed that most group B isolates expressed P1.7,16, P1.4, P1.5, P1.2, and P1.2.5 in most European countries (10). We found that 18% of cases were associated with P1.4. The six most prevalent serosubtypes in Scotland were responsible for 42 to 58% of all group B isolates (72 to 86% of serosubtypeable isolates) from 1994 to 1999. In the United States, six serosubtypes (P1.7,16, P1.19,15, P1.7,1, P1.5,2, P1.22a,14, and P1.14) were found in 54% of serosubtypeable group B isolates from 1992 to 1998 (24).

Although the serosubtypes (P1.7,16, P1.5,2, P1.19,15, P1.7, P1.5, and P1.1213) in the current hexavalent PorA OMP vaccine were associated with a majority of group B disease in The Netherlands, these serosubtypes accounted for only 9% of total isolates in Scotland. Wide diversity of PorA proteins and geographic differences in their prevalence pose major challenges to designing an effective group B vaccine for global use. Studies have shown that antibodies directed against immunodominance variable region of OMPs produced a broader protective immune response (6). Therefore, data on the characteristics of variable region in OMPs are needed in Scotland. Continued enhanced surveillance of the distribution of serogroups, serotypes, serosubtypes, the emergence of new clones of virulent meningococci, and the extent of cross-reactivity among the different OMPs could assist control strategies for epidemic outbreaks, the implementation of immunization policies, and the design of a vaccine for the prevention of meningococcal disease.

We thank microbiologists, Consultants in Public Health Medicine, and the staff of the Scottish Centre for Infection and Environmental Health for their help and cooperation with the study data.

REFERENCES

1. **Abdillahi, H., and J. Poolman.** 1987. Whole-cell ELISA for typing *Neisseria meningitidis* with monoclonal antibodies. FEMS Microbiol. Lett. **48:**367–371.
2. **Abdillahi, H., and J. Poolman.** 1988. Definition of meningococcal class 1OMP subtyping antigens by monoclonal antibodies. FEMS Microbiol. Immunol. **1:**139–144.
3. **Abdillahi, H., and J. Poolman.** 1988. *Neisseria meningitidis* group B serotyping using monoclonal antibodies in whole-cell ELISA. Microb. Pathog. **4:**27–32.
4. **Ashton, F., L. Mancino, and J. Ryan.** 1991. Serotypes and subtypes of *Neisseria meningitidis* serogroup B strains associated with meningococcal disease in Canada, 1977–1989. Can. J. Microbiol. **37:**623–627.
5. **Barquet, N., P. Domingo, J. A. Cayla, J. Gonzalez, C. Rodrigo, P. Fernandez-Viladrich, F. A. Moraga-Llop, F. Marco, J. Vazquez, J. A. Saez-Nieto, J. Canela, and M. Foz.** 1999. Meningococcal disease in a large urban population (Barcelona, 1987–1992). Arch. Intern. Med. **159:**2329–2340.
6. **Bash, M. C., F. Lynn, N. F. Concepcion, J. W. Tappero, G. M. Carlone, and C. E. Frasch.** 2000. Genetic and immunologic characterization of a novel serotype 4, 15 strain of *Neisseria meningitidis*. FEMS Immunol. Med. Microbiol. **29:**169–176.
7. **Borrow, R., H. Claus, M. Guiver, L. Smart, D. M. Jones, E. B. Kaczmarski, M. Frosch, and A. J. Fox.** 1997. Non-culture diagnosis and serogroup determination of meningococcal B and C infection by a sialytransferase (SiaD) PCR ELISA. Epidemiol. Infect. **118:**111–117.
8. **Cartwright, K., R. Morris, H. Rumke, A. Fox, R. Borrow, N. Begg, P. Richmond, and J. Poolman.** 1999. Immunogenicity and reactogenicity in UK infants of a novel meningococcal vesicle vaccine containing multiple class 1 (PorA) outer membrane proteins. Vaccine **17:**2612–2619.
9. **Caugant, D., L. Froholm, K. Bovre, E. Holten, C. E. Frasch, L. Mocca, W. D. Zollinger, and R. K. Selander.** 1986. Intercontinental spread of a genetically distinctive complex of clones of *Neisseria meningitidis* causing epidemic disease. Proc. Natl. Acad. Sci. USA **83:**4927–4931.
10. **Connolly, M., and N. Noah.** 1999. Is group C meningococcal disease increasing in Europe? A report of surveillance of meningococcal infection in Europe 1993–96. Epidemiol. Infect. **122:**41–49.
11. **Diermayer, M., K. Hedberg, F. Hoesly, M. Fischer, B. Perkins, M. Reeves, and D. Fleming.** 1999. Epidemic serogroup B meningococcal disease in Oregon. The evolving epidemiology of the ET-5 strain. JAMA **281:**1493–1497.
12. **Eldridge, J., E. Sutcliffe, J. Abbott, and D. Jones.** 1978. Serological grouping of meningococci and detection of antigen in cerebrospinal fluid by coagglutination. Med. Lab. Sci. **35:**63–66.
13. **Finne, J., M. Leinonen, and P. Makela.** 1983. Antigenic similarities between brain components and bacteria causing meningitis. Implications for vaccine development and pathogenesis. Lancet **ii:**355–357.
14. **Frasch, C., W. Zollinger, and J. Poolman.** 1985. Serotype antigens of *Neisseria meningitidis* and a proposed scheme for designation of serotypes. Rev. Infect. Dis. **7:**504–510.
15. **Kertesz, D. A., M. B. Coulthart, J. A. Ryan, W. M. Johnson, and F. E. Ashton.** 1998. Serogroup B, electrophoretic type 15 *Neisseria meningitidis* in Canada. J. Infect. Dis. **177:**1754–1757.
16. **Kieft, C., D. Martin, and M. Baker.** 2000. The epidemiology of meningococcal disease in New Zealand in 1999. Report prepared for the Ministry of Health by the Institute of Environmental Science and Research, Ltd. (ESR). New Zealand Ministry of Health, Wellington, New Zealand.
17. **Martin, S., R. Borrow, P. van der Ley, M. Dawson, A. Fox, and K. Cartwright.** 2000. Effect of sequence variation in meningococcal PorA outer membrane protein on the effectiveness of a hexavalent PorA outer membrane vesicle vaccine. Vaccine **18:**2476–2481.
18. **Perkins, B., K. Jonsdottir, H. Briem, E. Griffiths, B. Plikaytis, E. Hoiby, E. Rosenqvist, J. Holst, H. Nokleby, F. Sotolongo, G. Sierra, C. Huergo, G. Carlone, D. Williams, J. Dykes, D. Kapcznski, E. Tikhomirov, and J. Wenger.** 1998. Immunogenecity of two efficacious outer membrane protein-based serogroup B meningococcal vaccines among adults in Iceland. J. Infect. Dis. **177:**683–691.
19. **Pollard, A. J., and M. Levin.** 2000. Vaccines for prevention of meningococcal disease. Pediatr. Infect. Dis. J. **19:**333–345.
20. **Rosenstein, N. E., B. A. Perkins, D. S. Stephens, L. Lefkowitz, M. L. Cartter, R. Danila, P. Cieslak, K. A. Shutt, T. Popovic, A. Schuchat, L. H. Harrison, A. L. Reingold, and the Active Bacterial Core Surveillance Team.** 1999. The changing epidemiology of meningococcal disease in the United States, 1992–1996. J. Infect. Dis. **180:**1894–1901.
21. **Saachi, C., L. Pessoa, S. Ramos, L. G. Milagres, M. C. Camargo, N. T. Hidalgo, C. E. Melles, D. A. Caugant, and C. E. Frasch.** 1992. Ongoing group B *Neisseria meningitidis* epidemic in Sao Paulo, Brazil, due to increased prevalence of a single clone of the ET-5 complex. J. Clin. Microbiol. **30:**1734–1738.
22. **Scholten, R. J., H. A. Bijmer, J. T. Poolman, B. Kuipers, D. A. Caugant, L. V. Alphen, J. Dankert, and H. A. Valkenburg.** 1993. Meningococcal disease in the Netherlands, 1950–1990: a steady increase in the incidence since 1982 partially caused by new serotypes and subtypes of *Neisseria meningitidis*. Clin. Infect. Dis. **16:**237–246.
23. **Tikhomirov, E., M. Santamaria, and K. Esteves.** 1997. Meningococcal disease: public health burden and control. World Health Stat. Q. **50:**3–10.
24. **Tondella, M., T. Popovic, N. Rosenstein, D. Lake, G. Carlone, L. Mayer, and B. Perkins.** 2000. Distribution of *Neisseria meningitidis* serogroup B serotypes and serosubtypes in the United States. J. Clin. Microbiol. **38:**3323–3328.
25. **van Deuren, M., P. Brandtzaeg, and J. W. van der Meer.** 2000. Update of meningococcal disease with emphasis on pathogenesis and clinical management. Clin. Microbiol. Rev. **13:**144–166.
26. **Wedege, E., J. Kolberg, A. Delvig, E. Hoiby, E. Holten, E. Rosenqvist, and D. Caugant.** 1995. Emergence of a new virulent clone within the electrophoretic type 5 complex of serogroup B meningococci in Norway. Clin. Diagn. Lab. Immunol. **2:**314–321.
27. **World Health Organization.** 1999. Group A and C meningococcal vaccines. Wkly. Epidemiol. Rec. **74:**297–304.

Epidemiol. Infect. (2002), **128**, 149–156.
DOI: 10.1017/S0950268801006549 Printed in the United Kingdom

Prevalence of moderate penicillin resistant invasive *Neisseria meningitidis* infection in Scotland, 1994–9

M. H. KYAW[1 2]*, J. C. BRAMLEY[1], S. CLARKE[3], P. CHRISTIE[1], I. G. JONES[1] AND H. CAMPBELL[2]

[1] *Scottish Centre for Infection and Environmental Health, Clifton House, Clifton Place, Glasgow G3 7LN, UK*
[2] *Public Health Sciences, University of Edinburgh, Edinburgh, UK*
[3] *Scottish Meningococcus and Pneumococcus Reference Laboratory, Glasgow, UK*

(*Accepted 7 November 2001*)

SUMMARY

We examined the serological characteristics of 774 invasive meningococcal isolates collected through an active laboratory-based surveillance system in Scotland from 1994 to 1999. Of these, 72–73 % of isolates were tested for susceptibility to several antimicrobial agents. Meningococci with high-level resistance to sulphadiazine had a prevalence of 10 % and incidence of 0·22 per 100000 population. High-level resistance to penicillin and other antibiotics was not detected. The prevalence of moderate penicillin resistant meningococci was 8·3 %. There was no increase in moderate penicillin resistant meningococcal isolates during the study period, but there were temporal and geographic variations. The estimated incidence of moderate penicillin resistant meningococci was 0·15 per 100000 population. High and low incidence of moderate penicillin resistant meningococci appeared to correlate with the number of doses of penicillin prescribed in some geographic locations. The majority of moderate penicillin resistant isolates belonged to serogroups B (52·2 %) and C (39·2 %). However, the prevalence of moderate penicillin resistance in serogroup W135 was substantially higher (51·7 %) than serogroups B (7·8 %) and C (7·6 %). Serogroup W135 accounted for a higher proportion of moderate penicillin resistance (8·7 %) than disease (1 %). There was no predominant penicillin resistant serotype/subtype within any serogroup. Constant surveillance is necessary to monitor the emergence and spread of resistance and to guide appropriate public health interventions in preventing drug resistant meningococci.

INTRODUCTION

Neisseria meningitidis is an important cause of bacterial meningitis and septicaemia in the United Kingdom and worldwide [1, 2]. Despite the availability of effective antimicrobial agents, 10–20 % case-fatality and 20 % neurological sequelae ratios have been documented [3, 4]. Invasive meningococcal isolates that are resistant to penicillin have been detected in the United Kingdom, Europe and North America [5]. Surveys in the United Kingdom have shown that the prevalence of moderately resistant penicillin meningococcal isolates is increasing: 1–3 % in 1986/7, 8 % in 1991 [6, 7] and 11 % in 1995 [8]. A substantial increase has also been detected in Spain: from 0·4 % in 1985 to 46 % in 1990 [9], and to 67 % in 1996 [10]. In addition, meningococcal strains with high-level resistance to penicillin, through β-lactamase production, have been reported [11–13]. At present, high-level resistant isolates are extremely rare in the United Kingdom and elsewhere.

The failure of standard treatment in a patient with meningococcal disease caused by a penicillin resistant

* Author for correspondence.

strain (minimal inhibitory concentration (MIC) of 0·64 μg/ml) has been reported [14]. Since penicillin is the drug of first choice for the treatment of meningococcal disease, the emergence and spread of penicillin resistant meningococcal strains in the United Kingdom and other countries represents a major challenge. Little is known about the distribution of meningococcal serogroup, type and subtype in relation to penicillin resistance. Here, we examine the prevalence and seroepidemiology of penicillin resistant invasive meningococcal isolates reported to the active population-based surveillance system in Scotland during the period 1994–9.

METHODS

There has been an active population-based surveillance system for meningococcal disease in Scotland since the 1970s. However, the Scottish Meningococcus and Pneumococcus Reference Laboratory (SMPRL) was established in 1993 as the national service for the laboratory confirmation of meningococcal and pneumococcal disease and to monitor the epidemiological characteristics of these diseases, providing serotyping and antimicrobial susceptibility testing. We report on invasive meningococcal isolates submitted to the SMPRL from all diagnostic laboratories in Scotland for serological characterisation and antimicrobial susceptibility testing. Isolates from blood, cerebrospinal fluid (CSF), joint fluid and other sterile sites were regarded as invasive isolates.

Meningococcal isolates with a MIC level of $\leqslant 0·06$ μg/ml, 0·1–1 μg/ml, and $\geqslant 2$ μg/ml were regarded as susceptible, moderately and highly resistant to penicillin respectively. Meningococci were considered susceptible, moderately and highly resistant to sulphadiazine when their MICs were $\leqslant 16$ μg/ml, 32–64 μg/ml and $\geqslant 128$ μg/ml respectively. Isolates with MICs of $\leqslant 1$ μg/ml and $\geqslant 2$ μg/ml were indicated as susceptible and resistant to ciprofloxacin, cefotaxime, ceftriaxone and rifampicin respectively. During the study period, the E-test (Cambridge Diagnostics, Cambridge, UK) was used to determine the antimicrobial susceptibility level. The E-test has been proven to be a reliable method for evaluating the antimicrobial susceptibility levels of meningococci [15].

For the purpose of health service administration, Scotland (population 5·1 million) is divided into 15 health boards. The prevalence of antimicrobial resistant meningococci per 100000 population was calculated based on the estimated population of Scotland for the mid point year, 1997 [16]. Information on the number of doses of penicillin prescribed in the whole of Scotland between 1994 and 1999 was obtained from the Information and Statistics Division (ISD) of Common Services Agency, Edinburgh, Scotland. These data were used to calculate the number of penicillin doses prescribed per 100000 population and the number of penicillin resistant isolates in different geographical locations.

Statistical analysis

Data analyses were performed using SPSS version 10 and Stata (Stata Corporation, version 6.0, 1999, College Station, Texas). In comparisons between variables a P-value of $< 0·05$ was regarded as statistically significant.

RESULTS

A total of 774 invasive meningococcal isolates were received by SMPRL during the period 1994–9. Of these, antimicrobial susceptibility testing was performed for: 568 (73·4%) isolates for penicillin and sulphadiazine, 567 (73·3%) isolates for rifampicin, 563 (72·7%) isolates for ciprofloxacin and ceftriaxone, and 561 (72·5%) isolates for cefotaxine (Table 1). Of the 774 invasive isolates, serogroup B caused 400 (51·7%) cases of invasive disease, followed by group C with 303 (39·1%) cases, non-typeable group (NG) with 46 (5·9%) cases, W135 with 7 (1%) cases and other serogroups with 18 (2·3%) cases in 1994–9.

Antimicrobial resistant meningococci

The prevalence of antimicrobial resistance in invasive meningococcal infections in Scotland is shown in Table 1. The only drug to which any isolate was highly resistant was sulphadiazine (57 isolates, 10%). Forty-seven isolates (8·3%), 44 isolates (7·7%) and 1 isolate (0·2%) were moderately resistant to penicillin, sulphadiazine or ciprofloxacin respectively.

The estimated incidence of moderately resistant meningococci per 100000 population was 0·15. The rate of sulphadiazine resistance was 0·14 per 100000 population for moderately resistant isolates and 0·22 for highly resistant isolates.

Moderate resistance to penicillin by meningococcal serogroup

All isolates classed as moderately resistant to penicillin belonged to meningococcal serogroups B, C and

Table 1. *Prevalence of antimicrobial resistant invasive* N. meningitidis *infection in Scotland, 1994–9*

	No. (%) of isolates				Rate per 100000 population		
	Susceptible	Intermediate	Resistant	Total	Intermediate	Resistant	Total
Penicillin*	521 (91·9)	46 (8·1)	0 (0)	567 (100)	0·15	0	0·15
Sulphadiazine†	467 (82·3)	44 (7·7)	57 (10)	568 (100)	0·14	0·22	0·37
Ciprofloxacin‡	562 (99·8)	0 (0)	0 (0)	563†† (100)	0·003	0	0·003
Cefotaxime§	561 (100)	0 (0)	0 (0)	561 (100)	0	0	0
Ceftriaxone¶	563 (100)	0 (0)	0 (0)	563 (100)	0	0	0
Rifampicin**	567 (100)	0 (0)	0 (0)	567 (100)	0	0	0

* MICs: susceptible ⩽ 0·06 μg/ml; intermediate resistant, 0·1–1·0 μg/ml; resistant ⩾ 2 μg/ml.
† MICs: susceptible ⩽ 0·16 μg/ml; intermediate resistant, 32–64 μg/ml; resistant ⩾ 128 μg/ml.
‡ MICs: susceptible ⩽ 1 μg/ml; resistant ⩾ 2 μg/ml.
§ MICs: susceptible ⩽ 1 μg/ml; resistant ⩾ 2 μg/ml.
¶ MICs: susceptible ⩽ 1 μg/ml; resistant ⩾ 2 μg/ml.
** MICs: susceptible ⩽ 1 μg/ml; resistant ⩾ 2 μg/ml.
†† included one isolate with MIC = 1·5 μg/ml.

Table 2. *Prevalence of disease and moderate penicillin resistance in invasive* N. meningitidis *isolates by serogroups, 1994–9*

Year	B	C	W135	Others	Total
1994					
No. total tested	62	27	0	1	90
No. resistant	1	0	0	0	1
Resistant %	1·6	–	–	–	1·1
1995					
No. total tested	36	19	1	1	57
No. resistant	11	4	0	0	15
Resistant %	17·5	21·1	–	–	26·3
1996					
No. total tested	59	38	0	3	100
No. resistant	2	5	0	0	7
Resistant %	3·4	13·2	–	–	7
1997					
No. total tested	46	40	2	3	91
No. resistant	2	3	1	0	6
Resistant %	4·3	7·5	50	–	6·6
1998					
No. total tested	42	60	2	6	110
No. resistant	3	4	2	0	9
Resistant %	7·1	6·7	100	–	8·2
1999					
No. total tested	60	53	2	5	120
No. resistant	5	2	1	0	8
Resistant %	8·3	3·8	50	–	6·7
1994–9					
No. total tested	305	237	7	19	568
No. resistant	24	18	4	0	46
Resistant %	7·8	7·6	57·1	–	8·1

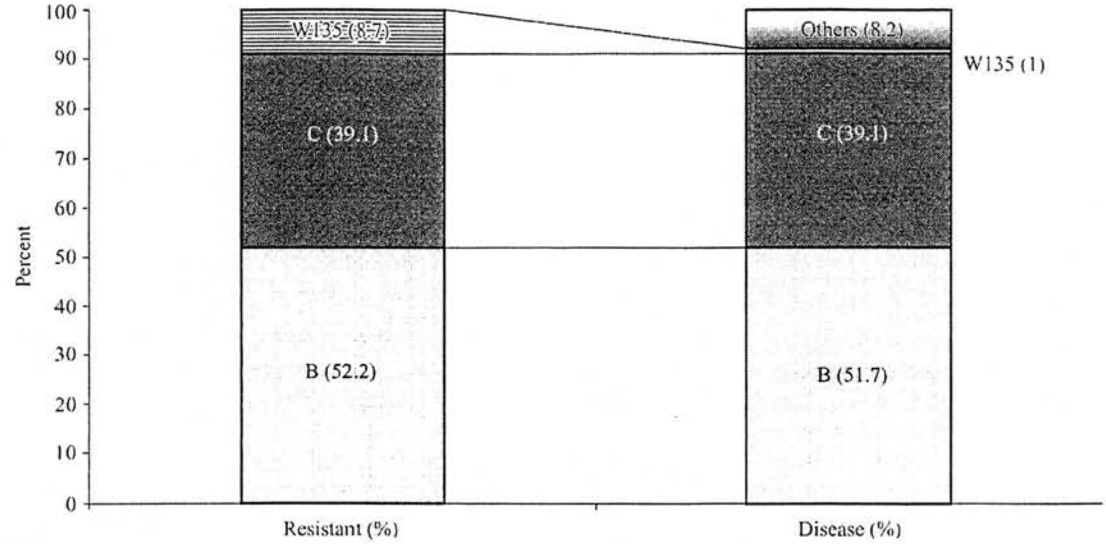


Fig. 1. Distribution of meningococcal serogroups in invasive disease and penicillin resistance, 1994–9.

Table 3. *Temporal and geographic distribution of relatively penicillin resistant invasive* N. meningitidis *isolates and pattern of penicillin prescribing in Scotland, 1994–9*

Laboratory	No (%) of penicillin resistant invasive isolates								No. doses penicillin prescribed	
Location*	1994	1995	1996	1997	1998	1999	Total 1994–9	Incidence rate†, 1994–9	No. of doses prescribed	Rate per 10^5 population
AC	–	2	1	1	2	1	7	0·27	62,770,675	$2·4 \times 10^5$
AA	–	1	2	–	–	1	4	0·18	50,728,780	$2·2 \times 10^5$
BR	–	–	–	–	–	–	–	–	13,329,784	$2·1 \times 10^5$
DG	–	–	–	–	–	1	1	0·11	19,005,257	$2·1 \times 10^5$
FF	–	–	–	–	1	–	1	0·05	49,252,019	$2·3 \times 10^5$
FV	–	1	–	–	1	1	3	0·18	35,266,571	$2·1 \times 10^5$
GR	–	1	–	1	–	–	2	0·06	69,884,948	$2·2 \times 10^5$
GG	1	2	3	1	–	2	9	0·17	151,186,546	$2·8 \times 10^5$
LN	–	3	1	2	3	1	10	0·30	93,133,697	$2·8 \times 10^5$
LO	–	1	–	1	–	1	3	0·06	106,646,135	$2·3 \times 10^5$
OR	–	–	–	–	–	–	–	–	2,277,914	$1·9 \times 10^5$
SH	–	–	–	–	1	–	1	0·72	2,766,403	$2·0 \times 10^5$
TY	–	2	–	–	–	–	2	0·08	55,193,772	$2·3 \times 10^5$
WI	–	–	–	–	–	–	–	–	3,148,540	$1·8 \times 10^5$
HI	–	2	–	–	1	–	3	0·24	26,958,029	$2·1 \times 10^5$
Scotland	1 (2·2)	15 (32·6)	7 (15·2)	6 (13·0)	9 (19·6)	8 (17·4)	46 (100)	0·15	741,549,070	$2·4 \times 10^5$

* AC, Argyll & Clyde; AA, Ayrshire & Arran; BR, Borders; DG, Dumfries & Galloway; FF, Fife; FV, Forth Valley; GG, Greater Glasgow; GR, Grampian; HI, Highland; LN, Lanarkshire; LO, Lothian; OR, Orkney; SH, Shetland; TY, Tayside; WI, Western Isley.

† Incidence rate per 100000 population.

W135 (Table 2). During 1994–9, as a whole, serogroup B was the predominant cause of invasive disease (51·7%) and of moderate resistance to penicillin (52·2%) (Fig. 1). This was followed by serogroup C, which accounted for 39·1% of invasive disease and of isolates with moderate resistance to penicillin. The proportion of isolates moderately resistant to penicillin and belonging to serogroup W135 (8·7%) was marked higher than the proportion of invasive disease due to serogroup W135 (1%) (Fig. 1). Indeed, the prevalence of moderate penicillin resistance in serogroup W135 was substantially higher (51·7%) than in serogroups B (7·8%) (p = 0·0001) and C (7·6%) ($P =$ 0·0001) (Table 2). Although an increasing trend for

Table 4. *Distribution of moderately penicillin resistant invasive meningococcal isolates by serogroup, type and subtype*

Serogroup B					Serogroup C					Serogroup W135				
Type/Subtype	Total no.	(rate*)	No. resistant	(rate*)	Type/subtype	Total no.	(rate*)	No. resistant	(rate*)	Type/subtype	Total no.	(rate*)	No. resistant	(rate*)
4:P1.4	44	(0·14)	5	(0·02)	2a:P1.2	27	(0·09)	4	(0·01)	NT:P1.3, 6	1	–	1	–
NT:P1.9	20	(0·07)	4	(0·01)	2a:P1.5	75	(0·24)	3	(0·01)	NT:P1.3, P1.6	1	–	1	–
NT:P1.16	9	(0·03)	3	(0·01)	2b:P1.16	7	(0·02)	3	(0·01)	NT:P1.6, P1.3	2	–	2	–
4:P1.15	9	(0·03)	2	–	2a:P1.2, 1·5	1	–	1	–					
1:P1.9	1	–	1	–	2a:P1.2, 5	15	(0·05)	1	–					
1:P1.14	13	(0·04)	1	–	2a:P1.10	2	–	1	–					
1:P1.16	1	–	1	–	2a:P1.2, P1.5	10	(0·03)	1	–					
15:P1.16	2	–	1	–	2b:P1.2	1	–	1	–					
15:P1.7, 16	13	(0·04)	1	–	2b:P1.2, 5	8	(0·03)	1	–					
21:P1.3, 1.6	1	–	1	–	NT:P1.12	1	–	1	–					
2b:NT	5	(0·02)	1	–	NT:NT	12	(0·04)	1	–					
NT:P1.4	10	(0·03)	1	–										
NT:NT	55	(0·18)	1	–										
NT:P1.15	11	(0·04)	1	–										

* Incidence per 100000 population.

moderate penicillin resistance caused by serogroup B was not consistent during the period 1994–9, a clear increase was noted from 3·4% in 1996 to 8·5–9·5% in 1998/9 (Table. 2). In contrast, the proportion of group C isolates which were moderately penicillin resistant decreased from 21·1% in 1995 to 3·8% in 1999. On the other hand, invasive meningococcal disease caused by serogroup C increased from 28·9% in 1994 to 52·6% in 1998 and to 46·5% in 1999. There was no increase in group B invasive meningococcal disease in the study period. No apparent change in the incidence of group W135 meningococcal disease or moderate penicillin resistance was noted between 1994 and 1999.

Temporal and geographic distribution of moderately penicillin resistant meningococci and the pattern of penicillin prescribing

Table 3 shows the temporal and geographic distribution of moderately penicillin resistant meningococci and pattern of penicillin prescribing in Scotland. There was no association between moderately penicillin resistant isolates and penicillin prescription rate across all health boards (Pearson correlation, $r = 0{\cdot}129$, $p = 0{\cdot}646$).

Serotype and subtype distribution of isolates in relation to moderately penicillin resistant invasive isolates

The serotype and subtype of invasive isolates moderately resistant to penicillin were diverse (Table 4). Twenty-four serotypes/subtypes in group B, 18 serotypes/subtypes in group C and 4 serotypes/subtypes in group W135 were found to have moderate resistance to penicillin. A higher proportion of isolates moderately resistant to penicillin had the serotype/subtype 4:P1.4, NT:P1.16, NT:P1.9 or 4:P1.15 in group B, and 2a:P1.2, 2a:P1.5 or 2b:P1.16 in group C. Three serogroup W135 isolates moderately resistant to penicillin were serotypes/subtypes NT:P1.3,6, NT:P1.3, P1.6, and NT:P1.6, P1.3. The incidence of disease or resistance was higher in type and subtype 4:P.14, NT:P1.9 and NT:P1.16 of group B and type and subtype 2a:P1.2 and 2a:P1.5 of group C.

DISCUSSION

Our study shows a low prevalence of invasive meningococcal isolates resistant to penicillin and other third generation antibiotics in Scotland between 1994 and 1999. Ten percent of isolates were highly resistant to sulphadiazine but no high level resistance was found to any other antimicrobial agents. High-level resistance to sulphadiazine could be due to the common use of sulphadiazine as chemoprophylaxis in close contacts of index patients during the 1950s to 1970s. However, isolates with resistance to penicillin, ciprofloxacin, ceflotaxime, ceftriaxone and rifampicin are of particular concern because they are generally used to treat patients with meningococcal meningitis and their close contacts. The failure to find any evidence of high level resistance to these antibiotics in the present study suggests that current antimicrobial agents remain effective in treating meningococcal disease. These data on antimicrobial resistance of meningococci are essential to inform guidelines on therapy for patients with meningococcal disease.

The annual incidence of moderately penicillin resistant meningococci was 0·15 per 100000 population. US data reported an incidence of 0·04 per 100000 population for moderate penicillin resistant meningococci in 1991 [17]. The prevalence of meningococci moderately resistant to penicillin was 8·3% and no evidence of an increase in moderate penicillin resistant isolates was observed during the study period. Previous studies have reported that the prevalence of penicillin resistant meningococci was 6% in Belgium in 1998 [18] and < 2% in the Netherlands [19]. A higher resistance rate was documented in England and Wales [8] and Spain [10]. Similar to our data, the US studies [17, 20] reported no overall increase in penicillin resistant meningococci during 1980s and 1990s. In contrast, a trend of increased resistance to penicillin among meningococci has been documented in England and Wales [6–8] and Spain [10, 21, 22].

The reason for geographic variation in prevalence of meningococcal isolates resistant to penicillin is not clear, but may be due to difference in MIC testing method. Similar to other meningeal bacterial pathogens such as *Streptococcus pneumoniae*, meningococcal disease requires treatment with antimicrobial agents. In addition, the rates of asymptomic carriage of meningococci and pneumococci are also similar in the population. However, the prevalence of penicillin resistance has been shown to increase globally for *Streptococcus pneumoniae* [23], and not for the meningococcus. Further studies are needed to address this issue. In common with evidence from Spain, geographic difference in the incidence of moderately penicillin resistant meningococci has been noted in the present study [22]. Although there was no statistical association, the areas with higher incidences of penicillin resistant meningococci tended to have higher penicillin prescribing rates. One study in Iceland noted that antimicrobial use was significantly related to nasopharyngeal colonisation with penicillin resistant pneumococci in children [24]. However, one survey from England suggested that an association between a high rate of antibiotic prescribing and a high incidence rate of meningococcal disease in some geographic locations might in part, be confounded by increased general practitioner consultation rates for lower respiratory infection [25]. Nevertheless it has been widely accepted that the selective pressure imposed by widespread use of antibiotics is likely to be responsible for the emergence and maintenance of antibiotic resistance [26].

Mechanisms leading to resistance are similar in gonococci and pneumococci [5]. Studies have also shown that the development of penicillin resistance in meningococci is due to altered forms of the penicillin-binding protein (PBP) gene resulting in reduced affinity for the antibiotics [22, 27, 28]. In addition, the emergence of penicillin resistant meningococci has been shown to occur by recruitment of a PBP gene from closely related species such as *Neisseria flavescens* [28]. It appears that antibiotic pressure combined with decreased affinities of penicillin binding proteins has been the primary factors for the development of resistant strains. Therefore, guidelines to limit the excessive usage of antibiotics will be helpful in controlling the emergence of resistance.

In England and Wales, meningococcal serogroups B and C were shown to be responsible for moderate penicillin resistance in 1985–9 [29]. We noted that serogroup B was associated with a higher proportion of penicillin resistance than group C and W135. This is consistent with previous reports in the US [17] and Spain [22]. In the present study, the prevalence of moderate penicillin resistance in meningococcal serogroup W135 was 57·1%. In addition, the proportion of resistant isolates contributed by serogroup W135 (8·7%) was substantially higher than the proportion of invasive disease caused by this serogroup in 1994–9. Recently, meningococcal serogroup W135 cases have been reported among pilgrims who had travelled to the Hajj in Mecca and their close contacts [30, 31]. Our data and this evidence confirm recent UK guidance on the advisability of offering all pilgrims the quadrivalent polysaccharide vaccine before traveling to Mecca.

Although meningococcal disease caused by serogroup C increased during the study period, there was no increase in the prevalence of penicillin resistance among serogroup C penicillin resistant isolates. One study in Spain also failed to show an associated increase in the prevalence of serogroup C penicillin resistance with an increase in serogroup C disease [32]. Similarly, we did not find any correlation between serogroup C meningococcal disease and penicillin resistant isolates.

In the United Kingdom, widespread use of meningococcal group C conjugate vaccine in November 1999 resulted in a rapid decline of group C disease in age-groups targeted for vaccination, with preliminary data showing a short-term efficacy of 97% for teenagers and 92% for toddlers [33]. In the present study, a higher proportion of meningococcal disease and penicillin moderately resistant isolates was caused by serogroup B. Our data reinforce the additional need for a vaccine against serogroup B meningococcal disease.

Our study shows a wide range of serotypes/subtypes in different serogroups among penicillin resistant isolates. Although group B serotypes/subtypes 4:P1.4 (16·7%) and NT:P1.16 (12·5%), group C serotypes/subtypes 2a:P1.2 (15·8%) and 2a:P1.5 (15·8%) were associated with a high proportion of moderate penicillin resistance, there was no clearly dominant serotype/subtype that was associated with penicillin resistance in a specific serogroup. Studies in Spain have shown conflicting results. One study found that group B serotype/subtype 4:P1.15 was associated with 51·4% of penicillin resistance and group C and non-serogroupable serotype type 2b were associated with 86% and 87% of penicillin resistance respectively [22]. However, an examination of 16 penicillin G-resistant strains in Spain failed to find a serotype specific association for penicillin resistant isolates [34]. We found that serogroups/types/subtypes B:4:P.14, B:NT:P1.9, B:NT:P1.16, C:2a:P1.2 and C:2a:P1.5 were associated with a higher proportion of resistance as well as disease. Due to the limited number of resistant isolates, caution should be taken in the interpretation of these data.

Our results show that at present the prevalence of penicillin resistant meningococci is low in Scotland, with marked geographic and temporal variations. The clinical importance of meningococci moderately resistant to penicillin is not clear, but meningococci with high-level resistance would have serious implications for patients with invasive disease. Since the prevalence of penicillin resistant meningococci could change rapidly, surveillance must be conducted continuously to detect any possible emergence of resistant meningococci. Further understanding of meningococcal sero-epidemiology and of the molecular characteristics of disease and penicillin resistance is critical for developing appropriate vaccines to control the disease and antibiotic resistance. Development of group B meningococcal vaccine will be critical in adding to the success of group C conjugate vaccination in the United Kingdom, as vaccination is the most effective method to control the spread of disease and the emergence of resistance.

ACKNOWLEDGEMENTS

We are most grateful to the staff at the microbiology laboratories in Scotland, in particular to Susan Brownlie, Barbara C. Denham, Dr L. Smart, Dr Giles Edwards, Jennifer Reid, Louise Thom, and Mathew Diggle for the help in the surveillance of meningococcal disease.

REFERENCES

1. Tikhomirov E, Santamaria M, Esteves K. Meningococcal disease: public health burden and control. World Health Stat Q 1997; **50**: 3–10.
2. Connolly M, Noah N. Is group C meningococcal disease increasing in Europe? A report of surveillance of meningococcal infection in Europe 1993–96. Epidemiol Infect 1999; **122**: 41–9.
3. Tzeng YL, Stephens DS. Epidemiology and pathogenesis of *Neisseria meningitidis*. Microbes Infect 2000; **2**: 687–700.
4. Pollard AJ, Levin M. Vaccines for prevention of meningococcal disease. Pediatr Infect Dis J 2000; **19**: 333–45.
5. Oppenheim BA. Antibiotic resistance in *Neisseria meningitidis*. Clin Infect Dis 1997; **24** (Suppl 1): S98–101.
6. Jones D, Kaczmarski E. Meningococcal infections in England and Wales: 1992. PHLS C D R Rev 1993; **3**: R129–31.
7. Jones D, Kaczmarski E. Meningococcal infections in England and Wales: 1994. PHLS C D R Rev 1995; **5**: R125–30.
8. Kaczmarski E. Meningococcal infections in England and Wales: 1995. CDR Rev 1997; **7**: R55–R59.
9. Saez-Nieto J, Vazquez J, Marcos C. Meningococci moderately resistant to penicillin. Lancet 1990; **336**: 54.
10. Pascual A, Joyanes P, Martinez-Martinez L, Suarez A, Perea E. Comparison of broth micro dilution and E-test for susceptibility testing of *Neisseria meningitidis*. J Clin Microbiol 1996; **34**: 588–91.
11. Dillon J, Pauze M, Yeung K-H. Spread of penicillinase-production and transfer plasmids from the gonococcus to *Neisseria meningitidis*. Lancet 1983; **i**: 779–81.
12. Botha P. Penicillin-resistant *Neisseria meningitidis* in southern Africa. Lancet 1988; **1**: 54.

13. Fontanals D, Pineda V, Pons I, Rojo J. Penicillin-resistant beta-lactamase-producing *Neisseria meningitidis* in Spain. Eur J Clin Microbiol Infect 1989; **8**: 90–1.
14. Turner P, Southern K, Spencer N, Pullen H. Treatment failure in meningococcal meningitis. Lancet 1990; **335**: 732–3.
15. Huges J, Biedenbach D, Erwin M, Jones R. E-test as susceptibility and epidemiological tool for evaluation of *Neisseria meningitidis* isolates. J Clin Microbiol 1993; **31**: 3255–9.
16. Information and Statistics Division (ISD). Scottish Health Statistic. UK (Edinburgh): ISD, 1999.
17. Jackson LA, Tenover FC, Baker C, et al. Prevalence of *Neisseria meningitidis* relatively resistant to penicillin in the United States. J Infect Dis 1994; **169**: 438–41.
18. Van ML, Carion F, Vandamme P, Goossens H. Surveillance of meningococcal disease in Belgium. Clin Microbiol Infect 1998; **4**: 224–8.
19. Goossens H, Sprenger MJ. Community acquired infections and bacterial resistance. BMJ 1998; **317**: 654–7.
20. Rosenstein NE, Stocker SA, Popovic T, et al. Antimicrobial resistance of *Neisseria meningitidis* in the United States. Clin Infect Dis 2000; **30**: 212–3.
21. Saez-Nieto J, Fontanals D, Jalon JGD, et al. Isolation of *Neisseria meningitidis* strains with increase of penicillin minimal inhibitory concentrations. Epidemiol Infect 1987; **99**: 463–9.
22. Saez-Nieto J, Lujan R, Berron S, et al. Epidemiological and molecular basis of penicillin resistant *Neisseria meningitidis* in Spain: a 5 years history (1985–1989). Clin Infect Dis 1992; **14**: 394–402.
23. Klugman K, Feldman C. Penicillin and cephalosporin-resistant *Streptococcus pneumoniae*. Emerging treatment for an emerging problem. Drugs 1999; **58**: 1–4.
24. Arason V, Kristinsson K, Sigurdsson J, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? BMJ 1996; **17**: 387–91.
25. Stuart J, Robinson P, Cartwright K, Noah N. Antibiotic prescribing during an outbreak of meningococcal disease. Epidemiol Infect 1996; **117**: 103–5.
26. Crook DW, Spratt BG. Multiple antibiotic resistance in *Streptococcus pneumoniae*. Brit Med Bull 1998; **54**: 595–610.
27. Mendelman P, Campos J, Chaffin D, et al. Relative penicillin G resistance in *Neisseria meningitidis* and reduced affinity of penicillin binding protein 3. Antimicro Agents Chemother 1988; **32**: 706–9.
28. Spratt BG, Zhang Q-Y, Jones DM, Hutchison A, Brannigan JA, Dowson CG. Recruitment of a penicillin-binding protein gene from *Neisseria flavescens* during the emergence of penicillin resistance in *Neisseria meningitidis*. Proc Natl Acad Sci 1989; **86**: 8988–92.
29. Jones D, Sutcliffe E. Meningococci with reduced susceptibility to penicillin. Lancet 1990; **335**: 863–4.
30. Communicable Disease Report Weekly. Meningococcal disease associated with the Haj–update. CDR Wkly 2000; **19**: 169.
31. Anonymous. Serogroup W135 meningococcal disease among travelers returning from Saudi Arabia–United States. MMWR 2000; **49**: 345–6.
32. Berron S, Vazquez J. Increase in moderate penicillin resistance and serogroup C in meningococcal strains isolated in Spain. Is there any relationship? Clin Infect Dis 1994; **18**: 161–5.
33. Ramsay ME, Andrews N, Kaczmarski EB, Miller E. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. Lancet 2001; **357**: 195–6.
34. Mendelman PM, Caugant DA, Kalaitzoglou G, et al. Genetic diversity of penicillin G-resistant *Neisseria meningitidis* from Spain. Infect Immun 1989; **57**: 1025–9.

PREVENTING PNEUMOCOCCAL DISEASE IN THE UNITED KINGDOM WITH PNEUMOCOCCAL VACCINES

M.H. Kyaw, Research Fellow, Scottish Centre for Infection and Environmental Health and Department of Public Health Sciences, University of Edinburgh; H. Campbell, Senior Lecturer, Department of Public Health Sciences, University of Edinburgh; I.G. Jones, Director, Scottish Centre for Infection and Environmental Health, Glasgow

INTRODUCTION

Disease caused by *Streptococcus pneumoniae* (the pneumococcus) is an important cause of avoidable morbidity and mortality in the UK.[1] It particularly affects very young children, the elderly and individuals with chronic systemic illnesses, including heart, lung and kidney disease, diabetes, immunosuppression, asplenia and alcoholism. These groups are predisposed to serious infections, including pneumonia, bacteraemia and meningitis. A recent paper has identified cigarette smoking as the strongest independent risk factor for invasive pneumococcal disease among immunocompetent, non-elderly adults.[2] The risk of invasive pneumococcal disease is particularly high in human immunodeficiency virus (HIV) infected persons, and is estimated to be 100- to 300-fold greater.[3] The A 23-valent polysaccharide vaccine is licensed for use in the UK, and a new 7-valent conjugate vaccine has recently obtained a licence in the US. This paper reviews the epidemiology of *S.pneumoniae* and the scope for disease prevention using polysaccharide or conjugate vaccines.

THE EPIDEMIOLOGY OF PNEUMOCOCCAL DISEASE

Pneumococcal disease is a major single cause of potentially vaccine preventable bacterial disease in the UK and other countries. Since it is not reportable, its precise incidence is unknown. Evidence suggests that 36-50% of community-acquired pneumonias are due to *S. pneumoniae*.[4, 5] The estimated annual incidences of pneumococcal pneumonia, bacteraemia and meningitis are 100 per 100,000, seven per 100,000 and 0.4 per 100,000 respectively in the UK,[4, 6] with corresponding case fatality rates of 5%, 20% and 30%.[7] Pneumococcal otitis media is also common in children under the age of five, among whom it has an estimated annual incidence of 40,000 per 100,000.[8, 9] The prevalence of penicillin and erythromycin resistant pneumococcal isolates has increased from <1% to 3.6–7.4% and from 5% to11% respectively during 1990/91 to 1997/98.[10] The increasing incidence of pneumococcal disease – largely due to the rise in numbers of elderly people, the global HIV pandemic, and multidrug resistant epidemic underscores the importance of pneumococcal infection as a significant public health problem.

Since *S. pneumoniae* was first isolated in 1880, this capsulated Gram-positive bacterium has been found to have at least 90 serotypes. The mucosal epithelium of the nasopharynx is the primary site of colonisation with risk of carriage depending on age, overcrowding and daycare centre attendance, breast feeding, season, smoking and prior antibiotic therapy.[11] The reported carriage rate is up to 60% in pre-school children, 25–35% in high school students, 18–29% in adults with children in household and 6% in adults without children in household.[12] The carriage rates in children in developing countries are two- or three-fold higher than in children in developed countries.[13] Nasopharyngeal colonisation is achieved by interaction between pneumococcal surface proteins and human epithelial cell receptors.[14] It occurs at some point in the first two years of life in most children.[15] The development of disease and spread of the pathogen are associated with nasopharyngeal colonisation.[16, 17]

The pneumococcus has three main surface layers; cell membrane, cell wall and capsule.[18] The polysaccharide capsule protects this bacterium from phagocytosis.[19] The level of pneumococcal virulence is based on the chemical composition of the capsule and varies considerably among the 90 known serotypes.[20, 21] Immunity to pneumococci depends on the production of serotype-specific protective antibody in response to capsular polysaccharide.[22, 23] Colonisation and development of antibody to relevant polysaccharide have been observed in military personnel and family members of persons with pneumonia.[24, 25]

Pneumococcal serotypes vary with age, source of specimens, geographic locations and time.[26-29] Between five and eight serogroups are responsible for at least 75% of invasive pneumococcal disease in children, and around ten or 11 in older children and adults in both developed and less developed countries.[30] Serogroups 4, 6, 9, 14, 18, 19 and 23 in young children, and 4, 6, 9, 12, 14, 19 and 23 in older children/adults, are more often associated with invasive disease in developed countries.[30] Types 1 and 5 are the most common causes of invasive pneumococcal disease in less developed countries.[28] In Scotland the most prevalent 11 serotypes and serogroups were, in numerical order, 14, 9, 19, 6, 23, 1, 3, 4, 7, 8 and 18, and these accounted for 84% of the total.[31] In addition, the prevalent serotypes causing mucosal and invasive infections are different. The data from the US showed that types 3, 19A and 23F, types 4, 9V, 14 and 18C, and type 6B were more frequently isolated from middle ear fluid, blood and cerebrospinal fluid (CSF) respectively.[27] Since the effectiveness of immunisation depends on the distribution of vaccine serotypes in the population being immunised,[28] a knowledge of the distribution of serogroups and serotypes is vital for vaccine policy in the prevention of invasive pneumococcal disease.

In 1967 the first isolate resistant to penicillin was reported from Australia, and the first multidrug-resistant pneumococci (resistant to three or more antimicrobial agents) from South Africa in 1977.[32, 33] Studies using molecular techniques have shown that the spread of only a few resistant clones account for the vast majority of resistant pathogens.[34] Evidence indicates that modern transport and the movement of people are responsible for the worldwide distribution of resistant mutants.[35] Pneumococcal serogroups 6, 9, 19 and 23 are the major causes of drug resistance world-wide, accounting for 80% of all pneumococcal resistant isolates.[36, 37] Nasopharyngeal colonisation with these strains is common in children and may play a major role in their spread.[17, 38, 39] Prior antibiotic

Proc R Coll Physicians Edinb 2001; **31**:124-133

use and daycare attendance correlate with increased antibiotic resistance in children under the age of five.[40,41] Geographic variation in the prevalence of drug resistance has been observed in Europe, North America, Asia and South Africa.[42] The highest penicillin resistance rates were reported from Hungary (58%)[43] and some countries in Asia (>70%).[44]

The high level penicillin resistance (minimal inhibitory concentration, MIC ≥2 mg/ml) in Scotland was very low, with only two serotype 14 (0.02%) blood isolates tested possessing this.[31] Penicillin intermediate resistance (MIC between 0.12 and 1.0mg/ml) accounted for 8% of isolates, most of which were serotype 14. In the US and other European countries, the most prevalent penicillin resistant serotypes are 23F, followed by 6, 14, and 19.[45] Studies from the US showed that a large proportion of penicillin resistant strains were also resistant to other antibiotics.[46,47] The molecular epidemiology of penicillin resistant pneumococci in 15 countries found that the 23F and 9V clones are responsible for global spread of drug resistant pneumococcal isolates.[48]

PNEUMOCOCCAL POLYSACCHARIDE VACCINE

Although a 14-valent pneumococcal polysaccharide vaccine was first licensed in the UK in 1979 and the 23-valent vaccine in 1989, the UK's Joint Committee on Vaccination and Immunisation (JCVI) did not recommend its use in vulnerable groups until 1992. The current 23-valent vaccine includes serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F and accounts for over 95% of invasive disease in the UK[49] and 88% in the US.[50] The current 23-valent polysaccharide covers above 95% of invasive disease in Scotland.[31]

The polysaccharide vaccine is effective in preventing 70–80% of invasive pneumococcal disease.[51,52] Based on this effectiveness, economic analysis from the US and Europe (including the UK) has suggested that pneumococcal vaccination would be a cost effective strategy for preventing invasive disease in the elderly.[53,54] In addition, the most frequently encountered global drug resistant isolates (6B, 9V, 14, 19A, 19F, 23F) of invasive pneumococcal disease are included in this vaccine.[42] Therefore, the increased use of polysaccharide vaccine may reduce the incidence of antibiotic susceptible and non-susceptible invasive pneumococcal disease. A single dose of the vaccine is currently recommended for those aged two years or older in whom pneumococcal infection is likely to be more common or more serious, including those with chronic cardiac disease, chronic pulmonary disease, chronic liver disease, chronic renal disease, diabetes mellitus, splenic dysfunction and immunodeficiency states.[55] The uptake of vaccine was estimated to be 5% in 1995 and 15% in 1998 among recommended groups in the UK.[56,57] Re-immunisation should be considered for persons at highest risk of pneumococcal disease, including those with asplenia, splenic dysfunction or the nephrotic syndrome. These individuals may need booster doses after five or ten years because of declining antibody levels.

Unfortunately, the current polysaccharide vaccine is poorly immunogenic in children under the age of two, the age group with the highest incidence of invasive and mucosal disease, and as a consequence it is not recommended for them. Moreover, the vaccine does not reduce carriage, and antibody levels fall over time.[58] Since polysaccharide antigens are T-cell independent, the vaccine is unable to induce immunological memory and protection is relatively short-lived.[59]

Four systematic reviews or meta-analyses of randomised controlled trials evaluating the effectiveness of immunisation with pneumococcal polysaccharide vaccine have been

TABLE 1
Conclusions of four systematic reviews or meta-analyses on the efficacy of pneumococcal polysaccharide vaccine.

Reference	Type of review	Conclusion
Fine MJ *et al.*[60]	Meta-analysis of nine trials published up to 1991	Pneumococcal vaccination appears efficacious in reducing bacteraemic pneumococcal pneumonia in low risk adults. However, evidence from randomised controlled trials fails to demonstrate vaccine efficacy for pneumococcal infection-related or other medical outcomes in the heterogeneous group of subjects currently labelled as high risk.
Watson L[61]	Systematic review and meta-analysis of 16 trials published up to March 1999	For studies carried out in the West, there was no protective effect found on mortality, all pneumonia or pneumococcal pneumonia, although there was a protective trend for pneumococcal bacteraemia, a surrogate outcome. In Third World studies, a significant protective effect was found for the three clinical outcomes.
Hutchison BG *et al.*[52]	Meta-analysis of 13 trials published up to November 1996	Vaccination with pneumococcal polysaccharide vaccine can be expected to reduce the risk of systemic infection due to pneumococcal types included in the vaccine by 83% and systemic infection due to all pneumococci by 73%. The vaccine was not less efficacious for the elderly, institutionalised people, or those with chronic disease.
Bandolier[62]	Systematic review of nine trials published up to 1999	Polysaccharide pneumococcal vaccines have yet to be shown to work in the types of people given them in industrialised countries. The only real evidence that they do comes from two improperly randomised studies from the 1940s.

carried out (Table 1).[52, 60, 62] Unfortunately, these papers reached differing conclusions, highlighting problems with meta-analysis which have been the subject of debate in journals.[63] Trials included had insufficient power to detect a number of different endpoints of relatively low incidence using vaccines of different composition. Due to study design problems in the published trials, expert reviewers have considered evidence from other case control and indirect cohort studies, and the current international consensus is that the vaccine can be considered to be 50–80% effective against invasive pneumococcal disease.[51, 64, 65] Although data from case control and indirect cohort studies have lower validity than those from randomised trials, it has been suggested that they offer logistical, ethical and statistical advantages in estimating the vaccine's effectiveness in patients with various high risk conditions.[66, 67] Tables 2 and 3 present the summaries of randomised trials, case control and indirect cohort studies conducted in the high risk groups. The current consensus of opinion from expert reviewers supports the recommendations of the JCVI to promote the uptake of pneumococcal polysaccharide vaccine for the prevention of invasive disease in at risk groups until the new conjugate vaccines become available in the UK.

CONJUGATE VACCINE

To address the inherent problems of polysaccharide vaccines, pneumococcal conjugate vaccines have been developed by coupling the capsular polysaccharides of the epidemiologically important serotypes to carrier proteins. The latter include tetanus toxoid, diphtheria toxoid, CRM_{197} (a non-toxic mutant of diphtheria toxin), pneumolysin or meningococcal outer membrane protein complex.[68] This has the effect of rendering the antigen T-cell dependent, leading to an anamnestic response to future infection.[69] Although the threshold antibody level which confers protection is unknown at present, pneumococcal conjugate vaccines elicit higher antibody responses than pneumococcal polysaccharide vaccines, induce mucosal antibody and immunologic memory and are likely to have a higher efficacy in preventing both invasive and non-invasive disease.[70] The conjugate pneumococcal vaccine contains 7 to 11 serotypes that cause the majority of pneumococcal disease in young children.[71] The 7-valent conjugate vaccine includes serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. In the 9-valent and 11-valent vaccines, serotypes 1 and 5 and serotypes 1,5, 3, and 7F are added respectively. In the US, the 7-valent vaccine would cover above 80% of invasive and 65% of non-invasive pneumococcal disease in children under six years of age.[27] The coverage of 9- to 11-valent vaccines covers serotypes causing 76–93% of invasive disease in children in the US and Europe.[72] A substantially lower coverage, 65–68%, of invasive isolates with 11-valent vaccine was observed in adults in developed countries.[30] In Scotland, the 7-, 9- and 11-valent conjugate vaccines would cover 61%, 68% and 80% of invasive pneumococcal isolates in all ages.[31]

Antibody responses to pneumococcal conjugate vaccines vary with serotypes and vaccine formulations.[71] Studies in developed and developing countries have reported that the pneumococcal conjugate vaccines are immunogenic in infants aged six to eight weeks.[70, 73] Antibody levels at seven months of age after a series of three doses range from 0.5 to 4.29 mg/ml for the poor immunogenic serotypes to 1.13 to 14.09 mg/ml for the most immunogenic serotypes.[70] It has been suggested that antibody levels of 0.3 mg/ml may afford protection against invasive disease caused by serotypes 3, 4, 6A, 8, 14, 19F and 23F in children.[74] Studies in patients with immunocompromised disorders[75, 78] (HIV, Hodgkin's and sickle cell diseases) and recurrent respiratory infections[79, 80] have shown that pneumococcal conjugate vaccines are capable of inducing higher antibody responses than the polysaccharide vaccine.

The first available data from a large scale double blind randomised controlled clinical trial in children have been reported from the three year Northern California Kaiser Permanente study among 37,000 children using Wyeth-Lederle's 7-valent pneumococcal CRM_{197} conjugate vaccine,[81] and the results of the Finnish efficacy trial for the prevention of pneumococcal otitis media are expected soon. Table 4 shows the vaccine efficacy in preventing various types of pneumococcal disease after immunisation at two, four, six and 12 to 15 months of age in the American study. The vaccine also appears to be safe and immunogenic. The adverse reactions to conjugate pneumococcal vaccines are minimal and comparable to the 23-valent polysaccharide vaccine and other routine paediatric vaccines.[71, 82-84]

The vaccine currently licensed in the US contains serotypes which are associated with multidrug resistant invasive strains.[42] Studies in other countries have shown a significant reduction in nasopharyngeal carriage in vaccinated infants and children.[85-87] Data from South Africa showed a reduction of 50% in nasopharyngeal carriage in vaccine serotypes in infants immunised at six, ten and 14 weeks.[87] This suggests that universal childhood vaccination with pneumococcal conjugate vaccine has the potential to produce herd immunity and decrease the spread of antibiotic resistant pneumococcal disease in children. Nevertheless, studies in South Africa and the Gambia found that colonisation with non-vaccine serotypes were increased in vaccines compared to controls.[85, 87] Therefore, continued surveillance data are essential to monitor the long-term colonisation effects of widespread use of conjugate vaccines in future.

Health economic studies in the US have concluded that infant immunisation with pneumococcal conjugate vaccine has the potential to be cost effective.[88, 89] If the vaccine costs were less than the manufacturer's list price of $58 for each dose, vaccination could even be cost saving.[88] The experience following the introduction of Hib vaccine in 1992 could therefore be repeated with pneumococcal conjugate vaccine (Figure 1).

The results of the US trial raise questions about the use of conjugate vaccine in adults. Unfortunately, the results are not directly applicable to older age groups for a number of reasons and the effectiveness of pneumococcal conjugate vaccines in preventing pneumonia and other respiratory infections, as well as their role in the elderly and high risk adults, require further examination. One problem is the more limited coverage of invasive disease serotypes in adults than in children, as noted above. Eight clinical studies of conjugate vaccines in adults have been reported.[58] Of these, six studies in younger adults showed that the conjugate vaccine produced higher antibody responses than the polysaccharide vaccine.[68, 78, 83, 90-92] In contrast to these findings, two other studies in persons

FIGURE 1
Laboratory reports of *Haemophilis influenzae* type B, Scotland 1988–99.

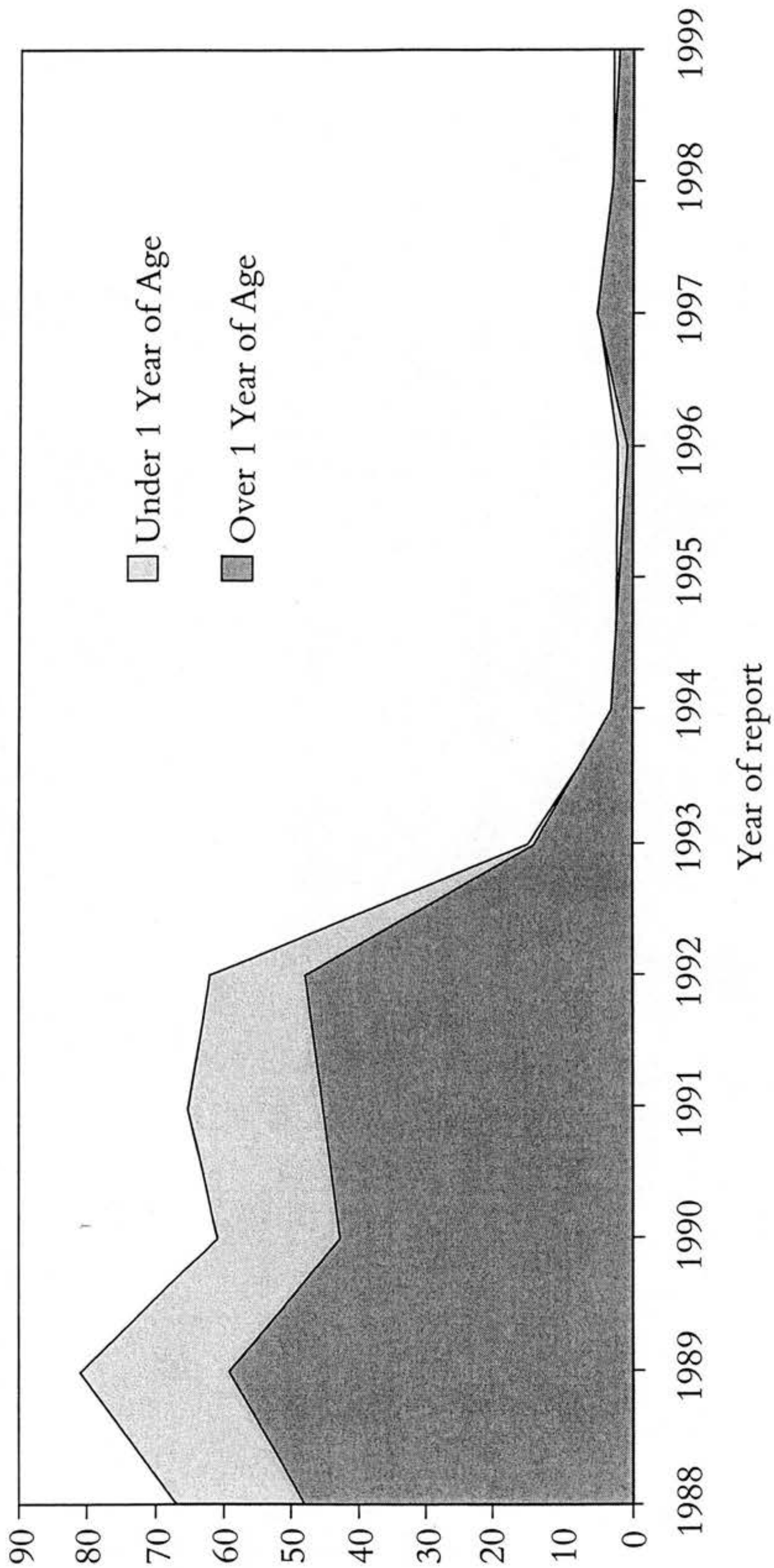


TABLE 2
Summary of randomised controlled trials conducted in high risk groups.

References	Trial site	Trial type	Characteristics of subjects	Outcome measure	Vaccine type	% efficacy (95% CI)	No. of subjects
Kaufman *et al.*[93]	US	Single blind	Institutionalised elderly	• Pneumonia • Bacteraemia	4-valent 4-valent	92 (72,98) 93 (45,100)	11,000
Austrian *et al.* (unpublished)	US	Single blind	Mentally ill elderly	• Pneumonia	12-valent	15 (<0,52)	1,300
Gaillet *et al.*[94]	France	Open	Nursing home residents	• Pneumococcal pneumonia	14-valent	77 (51,89)	1,686
Simberkoff *et al.*[95]	US	Double blind	Elderly	• Pneumonia • Bronchitis	14-valent 14-valent	<0 (<0,45)	2,295
Koivula *et al.*[96]	Finland	Double blind	Elderly	• Pneumococcal pneumonia	14-valent	59 (6, 82)	2,837
Ortqvist *et al.*[97]	Sweden	Double blind	Elderly	• Pneumonia • Pneumococcal pneumonia	23-valent 23-valent	-28(-150,34)	691
Macleod *et al.*[98]	US	Single blind	Military recruits	• Pneumonia	4-valent	85 (79,100)	17,035
Austrian *et al.*[99]	South Africa	Single blind	Gold miners	• Pneumonia • Bacteraemia	13-valent 13-valent	79 (65,88) 82 (66,92)	2,973
Smit *et al.*[100]	South Africa	Double blind	Gold miners	• Pneumonia • Pneumonia	6-valent 12-valent	76 (52,89) 92 (49,100)	3,019
Riley *et al.*[101]	Papua New Guinea	Double blind	Persons with age >10 years	• Bacteraemia	14-valent	86 (<0, 99)	11,958

TABLE 3

Summary of case-control and indirect cohort studies of pneumococcal vaccine effectiveness in high risk groups.

References	Outcome measure	% effectiveness (95%CI)	Location	No. of subjects
[2]Broome *et al.*[102]	Invasive infection	36*all ages (≥2 years) 60†(>10 years old) <0‡	US CDC (isolates from 46 hospitals in 26 States)	427/427
[1]Shapiro *et al.*[103]	Invasive infection	67† (13,87) (≥18 years) <0%‡	New Haven, US	90/90
[2]Bolan *et al.*[104]	Invasive infection	61* (1,85) (≥2years) 64‡ (47,76)	US CDC (isolates from 37 hospitals in 22 States)	1,887/1,887
[1,2]Forrester *et al.*[105]	Bacteraemia	<0* (<0,35) elderly	Denver, US	89/89
[1]Sims *et al.*[106]	Invasive infection	70† (37,86) elderly	Philadelphia, US	122/244
[1,2]Shapiro *et al.*[107]	Invasive infection	56 (42, 75)* (≥18 years) 61 (47, 72)† 21 (<0, 60)‡ 71 (30,88) elderly	Connecticut, US	983/983
[2]Butler *et al.*[50]	Invasive infection	57 (45,66)* (≥5 years) 49 (23,65)† 49 (22,64)‡ 75 (57,85) elderly	CDC (isolates from 54 hospitals in 26 States)	2,837/2,837
[1]Farr *et al.*[108]	Bacteraemia	81 (34,94)* (≥2 years)	Charlottesville, US	85/152
[2]Davidson *et al.*[109]	Invasive infection	79 (49,92)† adults	Alaska, US	87/87

1 case control study
2 indirect cohort study
* all conditions
† with underlying medical conditions (chronic lung, heart, liver, renal, diabetes mellitus and alcoholism)
‡ immunocompromised conditions (splenic disorders, sickle cell disease, haematological malignancies, organ transplant and systematic lupus erythematosus)

TABLE 4

Protective efficacy of 7-valent protein conjugate pneumococcal vaccine against invasive disease and otitis media.[81]

Analysis	Per protocol % (95% confidence interval)	Intention to treat % (95% confidence interval)
For serotypes contained in the vaccine, fully vaccinated, invasive disease	97·4 (82·7–99·9)	93·9 (79·6–98·5)
For all cases regardless of serotypes contained in the vaccine, invasive disease	–	89·1 (73·7–95·8)
Otitis media visits	8·9 (5·8–11·8)	7·8 (5·2–10·5)
Otitis media episodes	7·0 (4·1–9·7)	6·4 (3·9–8·7)
Frequent otitis (five episodes in six months/six in a year)	22·8 (6·7–36·2)	12·3 (0–23·2)
Ventilatory tube placement	20·1 (1·5–35·2)	20·3 (3·6–34·1)

aged 50 years and older did not show significant advantages in antibody responses over polysaccharide vaccine with the conjugate vaccine.[68, 83] Further studies are planned using different formulations and different schedules to assess the implications of conjugate vaccine for the prevention of pneumococcal disease in adults.

AREAS FOR FURTHER RESEARCH

Many questions which remain unanswered on pneumococcal immunisation need to be addressed. At this stage we do not know whether to recommend the polysaccharide or the conjugate vaccine for children over the age of two, nor under what circumstances or criteria. Will a course of conjugate vaccine require periodic boosting with conjugate or polysaccharide vaccine? Does the vaccine impair the immunological response to other childhood vaccines when given in the UK's accelerated immunisation schedule? Even more importantly, what effect would mass infant immunisation have on carriage among children and adults? Could this result in serotype displacement and the emergence of invasive or mucosal disease caused by serotypes not commonly associated with infection? Would the potential elimination of carriage result in ecological niches being filled with these other virulent strains of pneumococci or other organisms? Post-vaccine carriage studies of the kind currently being undertaken in relation to meningococcal C conjugate vaccine will be necessary to resolve this. Some of these questions are already the subject of current studies.

REFERENCES

1 Mayon-White R, editor. *The clinical impact of pneumococcal disease and strategies for its prevention.* London: The Royal Society of Medicine; 1995.

2 Nuorti J, Butler JC, Farley MM *et al.* Cigarette smoking and invasive pneumococcal disease. *NEJM* 2000; **342:**681-9.

3 Mao C, Harper M, McIntosh K *et al.* Invasive pneumococcal disease infections in human immunodeficiency virus-infected children. *J Infect Dis* 1996; **173:**870-6.

4 MacFarlane J. The clinical impact of pneumococcal disease. In: Mayon-White RT, editor. The clinical impact of pneumococcal disease and strategies for its prevention. *Royal Society of Medicine International Congress and Symposium Series* 1995; London Royal Society Medicine: **210:**9-17.

5 Kauppinen M, Herva E, Kujala P *et al.* The aetiology of community-acquired pneumonia among hospitalised patients during a *Chlamydia pneumoniae* epidemic in Finland. *J Infect Dis* 1995; **172:**1330-5.

6 Laurichesse H, Grimaud O, Waight P *et al.* Pneumococcal bacteraemia and meningitis in England and Wales, 1993 to 1995. *Communicable Disease and Public Health* 1998; **1:**22-7.

7 Breiman R, Spika J, Navarro V *et al.* Pneumococcal bacteremia in Charleston County, South Carolina a decade later. *Arch Intern Med* 1990; **150:**1401-5.

8 Teele D, Klein J, Rosner B *et al.* Epidemiology of otitis media during the first seven years of life in children in Greater Boston: a prospective, cohort study. *J Infect Dis* 1989; **160:**83-94.

9 Klein J. Otitis media. *Clin Infect Dis* 1994;**19:**823-33.

10 Reacher MH, Shah A, Livermore DM *et al.* Bacteraemia and antibiotic resistance of its pathogens reported in England and Wales between 1990 and 1998: trend analysis. *BMJ* 2000; **320:**213-6.

11 Ghaffar F, Friedland IR, Mccracken GH. Dynamics of nasopharyngeal colonization by *Streptococcus pneumoniae. Pediatr Infect Dis J* 1999; **18:**638-46.

12 Black S, Shinefield H. Issues and challenges: pneumococcal vaccination in pediatrics. *Ped Annals* 1997; **26:**355-60.

13 Greenwood B. The epidemiology of pneumococcal infection in children in the developed world. *Phil Trans R Soc Lond B* 1999; **354:**777-85.

14 Cundell D, Gerard N, Gerard C *et al. Streptococcus pneumoniae* anchor to activated human cells by the receptor for platelet-activating factor. *Nature* 1995; **377:**435-8.

15 Gray B, Turner M, Dillon HJ. Epidemiologic studies of *Streptococcus pneumoniae* in infants: the effects of season and age on pneumococcal acquisition and carriage in the first 24 months of life. *Am J Epidemiol* 1982; **116:**692-703.

16 Montgomery J, Lehmann D, Smith T *et al.* Bacterial colonization of the upper respiratory tract and its association with acute respiratory tract infections in Highland children of Papua New Guinea. *Rev Infect Dis* 1990; **12(suppl 8):**S1006-16.

17 Kellner J, McGeer A, Cetron MS *et al.* The use of *Streptococcus pneumoniae* nasopharyngeal isolates from healthy children to predict features of invasive disease. *Pediatr Infect Dis J* 1998; **17:**279-86.

18 Alonso de Velaasco E, Verheul A, Verhoef J *et al. Streptococcus pneumoniae*: virulence factors, pathogenesis and vaccines. *Microbiological Reviews* 1995; **59:**591-603.

19 Tuomanen EI, Austrian R, Masure HR. Pathogenesis of pneumococcal infection. *NEJM* 1995; **332:**1280-4.

20 Knecht J, Schiffman G, Austrian R. Some biological properties of pneumococcus type 37 and the chemistry of its capsular polysaccharide. *J Exp Med* 1970; **132:**475-87.

21 Lee C-J, Banks SD, Li JP. Virulence, immunity, and vaccine related to *Streptococcus pneumoniae. Critical Rev Microbiol* 1991; **18:**89-114.

22 Austrian R, Douglas R, Schiffman G *et al.* Prevention of pneumococcal pneumonia by vaccination. *Trans Assoc Am Physicians* 1976; **89:**184-94.

23 Musher D, Groover J, Rowland J *et al.* .Antibody to capsular polysaccharides of *Streptococcus pneumoniae*: prevalence, persistence, and antibody response. *Clin Infect Dis* 1993; **17:** 66-73.

24 Finland M, Tilghman R. Bacteriological and immunological studies of *Streptococcus pneumoniae* in infants: the development of type specific antibodies in healthy carriers. *J Clin Invest* 1936; **15:**501-8.

25 Musher D, Groover J, Reichler M *et al.* Emergence of antibody of capsular polysaccharides of *Streptococcus pneumoniae* during outbreaks of pneumonia: association with nasopharyngeal colonization. *J Infect Dis* 1997; **24:**441-6.

26 Nielsen S, Henrichsen J. Capsular types of *Streptococcus pneumoniae* isolated from blood and CSF during 1982–1987. *Clin Infect Dis* 1992; **15:**794-8.

27 Butler J, Breiman R, Lipman H *et al.* Serotypes distribution of *Streptococcus pneumoniae* infections among preschool children in the United States, 1978–1994: implications for development of a conjugate vaccine. *J Infect Dis* 1995; **171:**885-9.

28 Sniadack DH, Schwartz B, Lipman H *et al.* Potential interventions for the prevention of childhood pneumonia: geographic and temporal differences in serotype and serogroup distribution of sterile site pneumococcal isolates from children – implications for vaccine strategies. *Pediatr Infect Dis J* 1995; **14:**503-10.

29 Hausdorff WP, Bryant J, Kloek C *et al.* The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, Part II. *Clinical Infectious Diseases* 2000; **30:**122-40.

30 Hausdorff WP, Bryant J, Paradiso PR *et al.* Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, Part I. *Clinical Infectious Disease* 2000; **30:**100-21.

31 Kyaw MH, Clarke S, Edwards G *et al.* Serotypes/groups distribution and antimicrobial resistance of invasive pneumococcal isolates: implication for vaccine strategies. *Epidemiol Infect* 2000; **125:**561-72.

32 Hansman D, Bullen M. A resistant pneumococcus. *Lancet* 1967; **1:**264-5.

33 Jacobs M, Koornhof H, Robins-Browne R *et al.* Emergence of multiply resistant pneumococci. *N Eng J Med* 1978; **229:**735-40.

34 Cole KJ, Sniffen JC, Nadler JP, editors. Global epidemiology of antibiotic resistance. Program and abstracts from the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; San Francisco; 1999.

35 Soares S, Kristinsson K, Musser J *et al.* Evidence for the introduction of a multiresistant clone of serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the late 1980s. *J Infect Dis* 1993; **168:**158-63.

36 Klugman K. Pneumococcal resistance to antibiotics. *Clin Microbiol Rev* 1990; **3:**171-96.

37 Block S, Harrison C, Hedrick J *et al.* Penicillin-resistant *Streptococcus pneumoniae* in acute otitis media: risk factors, susceptibility patterns and antimicrobial management. *Pediatr Infect Dis J* 1995; **14:**751-9.

38 Dagan R, Yagupsky P, Goldbart A *et al.* Increasing prevalence of penicillin resistant pneumococcal infections in children in southern Israel: implications for future immunization policies. *Pediatr Infect Dis J* 1994; **13:**782-6.

39 Zenni M, Cheatham S, Thompson J *et al. Streptococcus pneumoniae* colonization in the young child: association with otitis media and resistance to penicillin. *J Pediatr* 1995; **127:**533-7.

40 Arnold K, Leggiadro R, Breiman R *et al.* Risk factors for carriage of drug-resistant *Streptococcus pneumoniae* among children in Memphis, Tennessee. *J Pediatr* 1996; **128:**757-64.

41 Dagan R, Melamed R, Muallem M *et al.* Nasopharyngeal colonization in southern Israel with antibiotic-resistant pneumococci during the first 2 years of life: relation to serotypes likely to be included in pneumococcal conjugate vaccines. *J Infect Dis* 1996; **174:**1352-5.

42 Appelbaum P. Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. *Clin Infect Dis* 1992; **15:**77-83.

43 Marton A, Gulyas M, Munoz R *et al.* Extremely high incidence of antibiotic resistance in clinical isolates of *Streptococcus pneumoniae* in Hungary. *J Infect Dis* 1991; **163:**542-8.

44 Song J-H, Lee NY, Ichiyama S *et al.* Spread of drug-resistance *Streptococcus pneumoniae* in Asian countries: Asian network for surveillance of resistant pathogens (ANSORP) study. *Clinical Infect Dis* 1999; **28:**1206-11.

45 Forward KR. The epidemiology of penicillin resistance in *Streptococcus pneumoniae. Semin Resp Infect* 1999; **14:**243-54.

46 Manson EJ, Kaplan S. Penicillin-resistant pneumococci in the United States (letter). *Pediatr Infect Dis J* 1995; **14:**1017-8.

47 Hofmann J, Cetron M, Farley M *et al.* The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. *N Engl J Med* 1995; **333:**481-6.

48 Hermans P, Sluijter M, Dejsirilert S *et al.* Molecular epidemiology of drug-resistant pneumococci: toward an international approach. *Micro Drug Resist* 1997; **3:**243-51.

49 George G. Epidemiology of pneumococcal disease. In: Mayon-White RT, editor. The clinical impact of pneumococcal disease and strategies for its prevention. *Royal Society of Medicine* 1995 (International Congress and Symposium Series 210):1-5.

50 Butler J, Breiman R, Campbell J *et al.* Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. *JAMA* 1993; **270:**1826-31.

51 Fedson DS. The clinical effectiveness of pneumococcal vaccination: a brief review. *Vaccine* 1999; **17:**S85-S90.

52 Hutchison BG, Oxman AD, Shannon HS *et al.* Clinical effectiveness of pneumococcal vaccine. Meta-analysis. *Can Fam Physician* 1999; **45:**2381-93.

53 Sisk JE, Moskowitz AJ, Whang W *et al.* Cost-effectiveness of vaccination against pneumococcal bacteraemia among elderly people. *JAMA* 1997; **278:**1333-9.

54 Ament A, Baltussen R, Duru G *et al.* The cost effectiveness of pneumococcal vaccination for older people: a study in five western European countries. *Clin Infect Dis* 2000; **31:**444-50.

55 Department of Health. *Immunisation against infectious disease.* London: HMSO; 1996.

56 McDonald P, Friedman E, Banks A *et al.* Pneumococcal vaccine campaign based in general practices. *BMJ* 1997; **314:**1094-8.

57 Kyaw M, Nguyen-Van-Tam J, Pearson J. Family doctor advice is the main determinant of pneumococcal vaccine uptake. *J Epidemiol Community Health* 1999; **53:**589-90.

58 Fedson D. Pneumococcal conjugate vaccination for adults: why it's important for children. *Pediatr Infect Dis J* 2000; **19:** 183-6.

59 Stein K. Thymus-independent and thymus-dependent responses to polysaccharide antigens. *J Infect Dis* 1992; **165(suppl):**S49-S52.

60 Fine MJ, Smith MA, Carson C *et al.* Efficacy of pneumococcal vaccination in adults: a meta-analysis of randomized controlled trails. *Arch Intern Med* 1994; **154:**2666-77.

61 Watson L. Effectiveness of pneumococcal polysaccharide vaccine: a systematic review and meta-analysis (MSc dissertation). University of Aberdeen; 1999.

62 Bandolier. Are pneumococcal vaccine effective? *Bandolier* 2000; **72:**72-4.

63 Bailar J. The promise and problems with meta-analysis. *N Engl J Med* 1997; **337:**559-61.

64 Wang E. *Administration of pneumococcal vaccine.* In: Canadian Task Force on the periodic Health Examination. Canadian Guide to Clinical Preventive Health Care. Ottawa: Health Canada; 1994; 386-95.

65 Morbidity and Mortality Weekly Report (MMWR). Prevention of pneumococcal disease: recommendations of the Advisory

Committee on Immunization Practices (ACIP). *MMWR* 1997; **46**:1-24.
[66] Clemens J, Shapiro ED. Resolving the pneumococcal vaccine controversy: are there alternatives to randomized clinical trials. *Reviews of Infectious Diseases* 1984; **6**:589-600.
[67] Fedson DS. Measuring protection: efficacy versus effectiveness. *Dev Biol Stand* 1998; **195**:195-201.
[68] Shelly M, Jacoby H, Riley G *et al.* Comparison of pneumococcal polysaccharide vaccine and CRM 197 conjugated pneumococcal oligosaccharide vaccines in young and elderly adults. *Infect Immun* 1997; **65**:242-7.
[69] Schneerson R, Barrera O, Sutton A *et al.* Preparation, characterization, and immunogenecity of *Haemophilus influenzae* type b polysaccharide-protein conjugates. *J Exp Med* 1980; **152**:361-76.
[70] Eskola J, Anttila M. Pneumococcal conjugate vaccines. *Pediatr Infect Dis J* 1999; **18**:543-51.
[71] Watson W. Pneumococcal conjugate vaccines. *Pediatr Infect Dis J* 2000; **19**:331-2.
[72] Fedson D, Musher D, Eskola J. Pneumococcal vaccine. In: Plotkin SA, Orenstein WA, editors. *Vaccines.* Philadelphia: W.B. Saunder Company; 1999; 553-607.
[73] Klein DL, Ellis RW. Conjugate vaccines against *Streptococcus pneumoniae.* In: Levine MM, Woodrow GC, Kaper JB *et al,* editors. *New generation vaccines.* Second edition. New York: Marcel Dekker Inc; 1997;503-25.
[74] Douglas R, Paton J, Duncan S *et al.* Antibody response to pneumococcal vaccination in children younger than five years of age. *J Infect Dis* 1983; **148**:131-7.
[75] Molrine D, Siber G, Tarbell N *et al.* Antibody responses to polysaccharide and polysaccharide-conjugate vaccines after treatment of Hodgkin's disease. *Ann Intern Med* 1995; **123**:828-34.
[76] Chan C, Morline D, Siber G *et al.* Pneumococcal conjugate vaccine primes for antibody responses to polysacharide pneumococcal vaccine after treatment of Hodgkin's disease. *J Infect Dis* 1996; **173**:256-8.
[77] King JC, Vink PE, Chang IH *et al.* Antibody titers eight months after three doses of a 5-valent pneumococcal conjugate vaccine in HIV and non-HIV-infected children less than two years of age. *Vaccine* 1998; **16**:361-5.
[78] Vernacchio L, Neufeld EJ, MacDonald K *et al.* Combined schedule of 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal vaccine in children and young adults with sickle cell disease. *J Pediatr* 1998; **133**:275-8.
[79] Sorensen R, Leiva L, Giangrosso P *et al.* Response to a heptavalent conjugate *Streptococcus pneumoniae* vaccine in children with recurrent infections who are unresponsive to the polysaccharide vaccine. *Pediatr Infect Dis J* 1998; **17**:685-91.
[80] Barnett E, Pelton S, Cabral H *et al.* Immune response to pneumococcal conjuagte and polysaccharide vaccines in otitis-prone and otitis-free children. *Clin Infect Dis* 1999; **29**:191-2.
[81] Black S, Shinefield H, Fireman B *et al.* Efficacy, safety and immunogenecity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* 2000; **19**:187-95.
[82] Leach A, Ceesay SJ, Banya WAS *et al.* Pilot trial of a pentavalent pneumococcal polysaccharide/protein conjugate vaccine in Gambian infants. *Pediatr Infect Dis J* 1996; **15**:333-9.
[83] Powers D, Anderson E, Lottenbach K *et al.* Reactogenicity and immunogenicity of a protein conjugated pneumococcal oligosoccharide vaccine in older adults. *J Infect Dis* 1996; **173**:1014-8.
[84] Shinefield H, Black S, Ray P. Safety and immunogenecity of heptavalent pneumococcal CRM197 conjugate vaccine in infants and toddlers. *Pediatr Infect Dis J* 1999; **18**:757-63.
[85] Obaro S, Adegbola R, Banya W *et al.* Carriage of pneumococci after pneumococcal vaccine. *Lancet* 1996; **348**:271-2.
[86] Dagan R, Muallem M, Melamed R *et al.* Reduction of pneumococcal nasopharyngeal carriage in early infancy after immunization with tetravalent pneumococcal vaccines conjugated to either tetanus toxoid or diphteria toxoid. *Pediatr Infect Dis J* 1997; **16**:1060-4.
[87] Mbelle N, Huebner RE, Wasas AD *et al.* Immunogenecity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. *J Infect Dis* 1999; **180**:1171-6.
[88] Lieu TA, Ray GT, Black SB *et al.* Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children. *JAMA* 2000; **283**:1460-8.
[89] Hueston W, Mainous A, Brauer N. Predicting cost-benefits before programs are started: looking at conjugate vaccine for invasive pneumococcal infections. *J Community Health* 2000; **25**:23-33.
[90] Ahmed F, Steinhoff M, Rodriguez-Barradas M *et al.* Effect of human immunodeficiency virus type 1 on the antibody response to a glycoprotein conjugate pneumococcal vaccine: results from a randomised trial. *J Infect Dis* 1996; **173**:83-90.
[91] Vidarsson G, Sigurdardottir S, Gudnason T *et al.* Isotypes and opsonophagocytosis pneumococcus type 6B antibodies elicited in infants and adults by an experimental pneumococcus type 6B-tetanus toxoid vaccine. *Infect Immun* 1998; **66**:2866-70.
[92] Soininen A, Seppala I, Nieminen T *et al.* IgG subclass distribution of antibodies after vaccination of adults with pneumococcal conjugate vaccines. *Vaccine* 1999; **17**:1889-97.
[93] Kaufman P. Pneumonia in old age. Active immunization against pneumonia with pneumococcus polysaccharide: results of a six-year study. *Arch Intern Med* 1947; **79**:518-31.
[94] Gaillat J, Zmirou D, Mallaret MR *et al.* Essai Clinique du vaccin antipneumococcique chez personnes agees vivant en institution. *Rev Epidemiol Sante Publique* 1985; **33**:437-44.
[95] Simberkoff M, Cross A, Al-lbrahim M *et al.* Efficacy of pneumococcal vaccine in high-risk patients. Results of a Veterans Administrative Cooperative Study. *N Engl J Med* 1986; **315**:1318-27.
[96] Koivula I, Sten M, Makela P. Clinical efficacy of pneumococcal vaccine in the elderly: a randomized, single-blind population-based trail. *Am J Med* 1997; **103**:281-90.
[97] Ortqvist A, Hedlund J, Burman A *et al.* Randomized trial of 23-valent pneumococcal capsular polysaccharide vaccine in the prevention of pneumonia in middle-aged and elderly people. *Lancet* 1998; **351**:399-403.
[98] Macleod C, Hodges R, Heidelberger M *et al.* Prevention of pneumococcal pneumonia by immunization with specific capsular polysaccharides. *J Exp Med* 1945; **82**:445-65.
[99] Austrian R. Vaccines of pneumococcal capsular polysaccharides and the prevention of pneumococcal pneumonia, in the role of immunological factors in infectious, allergic, and autoimmune processes. In: Basset RJ, editor. *The role of immunological factors in infectious allergic and autoimmune processes.* New York: Raven Press; 1976; 79-89.
[100] Smit P, Oberholzer D, Hayden-Smith S *et al.* Protective efficacy of pneumococcal polysaccharide vaccines. *JAMA* 1977; **238**:2613-6.
[101] Riley I, Tarr P, Andrew M *et al.* Immunisation with a polyvalent pneumococcal pneumonia. Reduction of adult respiratory mortality in a New Guinea Highlands community. *Lancet* 1977; **1**:1338-41.
[102] Broome C, Facklam R, Fraser D. Pneumococcal disease after pneumococcal vaccination. An alternative method to estimate the efficacy of pneumococcal vaccine. *N Engl J Med* 1980; **303**:549-52.
[103] Shapiro E, Clemens J. A controlled evaluation of the protective efficacy of pneumococcal vaccine for patients at high risk of serious pneumococcal infection. *Ann Intern Med* 1984; **101**:325-30.
[104] Bolan G, Broome C, Facklam R *et al.* Pneumococcal vaccine efficacy in selected populations in the United States. *Ann Intern Med* 1986; **104**:1-6.
[105] Forrester H, Jahnigen D, LaForce F. Inefficacy of

pneumococcal vaccine in high-risk population. *Am J Med* 1987; **83**:425-30.
[106] Sims R, Steinmann W, McComville J *et al.* The clinical effectiveness of pneumococcal vaccine in the elderly. *Ann Intern Med* 1988; **108**:653-7.
[107] Shapiro E, Berg A, Austrian R *et al.* The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Eng J Med* 1991; **325**:1453-60.
[108] Farr B, Johnston B, Cobb D *et al.* Preventing pneumococcal bacteraemia in patients at risk. Results of matched case-control study. *Arch Intern Med* 1995; **155**:2336-40.
[109] Davidson M, Parkinson AJ, Bulkow L *et al.* Epidemiology of invasive pneumococcal disease: reply. *J Infect Dis* 1995; **171**:1065-6.

Acta Pædiatr 90: 473–476. 2001

VIEWPOINT ARTICLE

Prevention of pneumococcal disease in children. Pneumococcal conjugate vaccines: their use globally could have a major impact on public health

MH Kyaw[1,2], IG Jones[2] and H Campbell[1]

University of Edinburgh, Public Health Sciences[1], Edinburgh; Scottish Centre for Infection and Environmental Health[2], Glasgow, Scotland

Kyaw MH, Jones IG, Campbell H. Prevention of pneumococcal disease in children. Pneumococcal conjugate vaccines: their use globally could have a major impact on public health. Acta Pædiatr 2001; 90: 473–476. Stockholm. ISSN 0803-5253

Pneumococcal disease is a major cause of morbidity and mortality in infants and young children worldwide. New pneumococcal conjugate vaccines include 7 to 11 serotypes, which are the most common cause of paediatric disease in most parts of the world. The efficacy of a 7-valent conjugate vaccine was 97.4% (95% CI, 82.7–99.9) against invasive pneumococcal disease, and 57% (95% CI, 44–67) against otitis media, caused by vaccine serotypes. Evidence shows that the vaccine has the potential to prevent pneumonia. Pneumococcal conjugate vaccination has also been shown to reduce nasopharyngeal carriage of vaccine serotypes (particularly serotypes associated with antibiotic resistance). Thus widespread use of pneumococcal conjugate vaccine could substantially reduce the burden of invasive disease and would have the potential to control the global spread of antibiotic resistance in pneumococci.

Conclusion: It is important that these highly effective vaccines should be made available to children in the developing countries.

Key words: *Conjugate vaccines, developing countries, disease prevention, pneumococcus*

Moe H. Kyaw, Scottish Centre for Infection and Environmental Health, Clifton House, Clifton Place, Glasgow G3 7LN, Scotland (Tel. +44 (0)141 300 1184, e-mail. Moe.Kyaw@scieh.csa.scot.nhs.uk

The pneumococcus is a major cause of pneumonia, bacteraemia, meningitis and otitis media in children under 5 y of age. The World Health Organization (WHO) has estimated that 1.2 million children under 5 y of age die annually as a result of pneumococcal disease (1). More than 70% of pneumococcal disease in children occurs before the age of 2 y (2–4). Data from the US and Europe indicate that the estimated annual incidence rates per 100000 young children are 700 for pneumococcal pneumonia (5–8), 10 for pneumococcal meningitis (9, 10), 20 to 140 for pneumococcal bacteraemia (9, 10) and 40000 for pneumococcal otitis media (11–13). The available 23-valent pneumococcal polysaccharide vaccine has been shown to reduce invasive bacterial infections by 50–70% in children older than 2 y of age (14, 15). However, the vaccine is poorly immunogenic in children under 2 y, particularly against serotypes 6A, 14, 18C, 19F and 23F (16, 17). Pneumococcal isolates resistant to penicillin and other antibiotics are gradually increasing worldwide (18), with the prevalence of resistant isolates as high as 80% (in Asia) (19). This significant morbidity and mortality together with the growing spread of (multi) drug-resistant isolates emphasizes the clear need for effective new vaccines against pneumococcal disease.

The spectacular success of the *Haemophilus influenzae* type b (Hib) conjugate vaccine, which has almost eradicated serious disease caused by Hib in countries where universal vaccination has been introduced, suggests that it may be possible to achieve a similar outcome with an effective conjugate pneumococcal vaccine. Linking a protein carrier to pneumococcal polysaccharides has been shown to increase immunogenicity in both primary and booster doses in young children by producing a vaccine that evokes a T cell-dependent immune response (20, 21). The results from ongoing multicentre clinical trials in developed and less-developed countries suggest that pneumococcal conjugate vaccines will be safe and immunogenic in infants and children (22–28).

The current 7-valent conjugate vaccine (which includes serotypes 4, 14, 6B, 19F, 18C, 23F and 9V) covers 86% and 83% of pneumococcal serotypes that cause pneumococcal bacteraemia and meningitis, respectively, in the US (29). The 9- and 11-valent conjugate vaccines, which include serotypes 1 and 5 and 1, 3, 5 and 7F, respectively, cover an estimated 73–92% of invasive pneumococcal disease in the developed countries (15). An extensive analysis of recent data from Latin America, Europe and North America indicates that the serogroups included in 9-valent and 11-valent conjugate vaccines cover 60% or more of all pneumococcal isolates from pneumonia patients, both young children and older children (30). The 7-valent conjugate vaccine serotypes account for 65% of otitis media in the US (29, 31) and 56% of otitis media in Israel (32). Furthermore, serogroups 3, 19, and 23, which are major causes of otitis media in young children in the US, Canada and Europe, are included in the 11-valent conjugate vaccine (30).

Significant geographical variation in serotype distribution of prevalent pneumococcal isolates that cause invasive pneumococcal infections has been reported. Serotypes 1 and 5 are the most common causes of invasive pneumococcal disease among children less than 2 y of age in Africa and Asia but not in Western Europe and North America (33). Seroepidemiological data indicate that the proportion of isolates which belong to a serogroup contained in the 7 to 11-valent conjugate vaccines covers only approximately 20–55% of isolates from cases of meningitis in Asian countries (30). Differences in serotype distribution and seroepidemiology of disease among regions and countries could lead in the future to the development of pneumococcal conjugate vaccines with different serotype constituents.

Pneumococcal conjugate vaccines elicit higher antibody responses than pneumococcal polysaccharide vaccines (21). The threshold antibody level that confers protection is unknown at present, although evidence from Hib conjugates implies that pneumococcal conjugate vaccines will have a higher efficacy than polysaccharide vaccines in preventing both invasive and non-invasive pneumococcal disease. The first available data from a large-scale clinical trial in Northern California, conducted among 37 868 children using the 7-valent Pnc-CRM197 conjugate vaccine, were shown to have 97.4% efficacy (95% CI, 82.7–99.9) in preventing invasive pneumococcal disease caused by vaccine serotypes after immunization at 2, 4, 6 and 12–15 mo of age (31). The reported serotype-specific efficacy of pneumococcal conjugate vaccine against otitis media was 57% (95% CI, 44–67) in the Finnish study (34). The US trial found a reduction in episodes of pneumonia in conjugate vaccine recipients: efficacy of 11.4% (95% CI, 1.3–20.5) against clinical pneumonia, 33.0% (95% CI, 7.3–51.5) against X-ray-confirmed pneumonia, and 73.1% (95% CI, 38–88.3) against consolidation ($\geq$2.5 cm on X-ray) (35). Pneumococcal conjugate vaccine appears to be safe and immunogenic (36). Children with HIV infection (37, 38), Hodgkin's disease (39) and sickle cell disease (40, 41) also show improved immune responses with this vaccine compared with the pneumococcal polysaccharide vaccine.

Pneumococcal serotypes (6B, 9V, 14, 19A (19F), 23F), which are closely associated with multidrug-resistant strains associated with invasive disease in children in many countries, are included in the 7-valent vaccine (18). Studies from Gambia (42), Israel (25) and South Africa (28) have shown a significant reduction in nasopharyngeal carriage in vaccinated infants and children. This suggests that widespread vaccine use (coverage above 90%) may produce herd immunity by reducing transmission of the pneumococcus and thus risk of infection. Therefore, universal childhood vaccination with pneumococcal conjugate vaccine has the potential to decrease the spread of pneumococcal serogroups included in the vaccine (which includes the major serogroups associated with antibiotic resistance). Reduced carriage of pneumococcal vaccine serotypes, particularly resistant serotypes, has been observed in vaccinees (25, 28). Nevertheless, replacement of vaccine serotypes by non-vaccine serotypes has been reported (42, 28). In a recent Finnish otitis media trial, an increase in disease caused by non-vaccine serotypes was documented (34). It is uncertain whether this indicates true serotype replacement, or the "unmasking" of less-prevalent serotypes due to elimination of dominant serotypes by conjugate vaccine. Interestingly, a large-scale US study, so far, did not observe the emergence of non-vaccine serotypes in place of the vaccine serotypes (31).

In less-developed countries, the highest incidence of invasive pneumococcal infections is in the first 6 mo of life (4). Since any new pneumococcal conjugate vaccine is likely to be introduced into the childhood immunization schedules at 2/4/6 or 2/3/4 mo of age, there will be a need for complementary immunization strategies. These include maternal immunization with 23-valent polysaccharide vaccine, to protect infants under 6 mo of age. The administration of pneumococcal polysaccharide vaccines during the third trimester of pregnancy has been shown to be safe, and to produce infant/maternal antibody responses in serum and breast milk (43–45). Studies from the US and Papua New Guinea show that passively acquired pneumococcal antibodies could prevent 30% of serious pneumococcal infections in early infancy and childhood (43, 46). Maternal immunization may therefore be a feasible strategy in reducing infant morbidity and mortality from pneumococcal infection in the less-developed countries and merits further research. Current research priorities include further evaluation of the reduction in nasopharyngeal carriage associated with vaccination, seeking evidence of replacement of vaccine serotypes by non-vaccine serotypes and investigating the nature of herd immunity associated with pneumococcal conjugate vaccines.

The new pneumococcal conjugate vaccines will be expensive. The reported cost of a course of the recently licensed 7-valent vaccine in the US is currently more than $230 (47). At a cost of US $58 per dose, universal vaccination with pneumococcal conjugate vaccine would cost society $80000 per life saved, $3200 per case of pneumonia prevented, $160 per episode of otitis media prevented, $280000 per meningitis case prevented and $15000 per bacteraemia case prevented (47). With the increasing number of childhood vaccines, it is possible that some health systems will respond by seeking to give priority to some vaccines in order to manage the escalating costs of healthcare, even in developed countries. However, in the context of the total costs of healthcare, the costs of childhood vaccines remain small. Nevertheless, less-developed countries will not be able to afford to include them in their routine childhood immunization programmes. The situation may be similar to Hib vaccines, where routine use in less-developed countries remains extremely limited, despite clear evidence of the (cost) effectiveness of vaccination (48, 49).

Pneumococcal conjugate vaccines have the potential to save the lives of more than one million children under 5 y of age annually, worldwide. By eliminating nasopharyngeal carriage in vaccinated children, they could possibly control the global spread of antibiotic-resistant isolates and the incidence of pneumococcal infections among persons with HIV in Asia and Africa. Consequently, there is likely to be a strong public health case for pneumococcal conjugate vaccines to be made available for use in less-developed countries. The motivation of rich countries to invest in the control of pneumococcal disease worldwide and the reduction of global childhood mortality from pneumococcal disease remains to be determined.

References

1. World Health Organisation (WHO). Vaccine research and development: report of the technical review group meeting, June 9–10, 1997. Geneva: WHO, 1997: 32–6
2. Gray B, Converse G, Dillion HJ. Epidemiologic studies of Streptococcus pneumoniae in infants: acquisition, carriage, and infection during the first 24 months of life. J Infect Dis 1980; 142: 923–33
3. Wenger JD, Hightower AW, Facklam RR, Gaventa S, Broome CV. Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. J Infect Dis 1990; 162: 1316–23
4. Levine MM, Lagos R, Levine OS, Heitmann I, Enriquez N, Pinto ME, et al. Epidemiology of invasive pneumococcal infections in infants and young children in metropolitan Santiago, Chile, a newly industrializing country. Pediatr Infect Dis J 1998; 17: 287–93
5. Foy HM, Cooney MK, McMahan R, Grayston JT. Viral and mycoplasmal pneumonia in a prepaid medical care group during an eight year period. Am J Epidemiol 1973; 97: 93–102
6. Paisley JW, Lauer BA, McIntosh K, Glode MP, Schachter J, Rumack C. Pathogens associated with acute lower respiratory tract infection in young children. Pediatr Infect Dis J 1984; 3: 14–9
7. Jokinen C, Heiskannen L, Juvonen H, Kallinen S, Karkola K, Korkola M, et al. Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. Am J Epidemiol 1993; 137: 977–88
8. Heiskanen-Kosma T, Korppi M, Jokinen C, Kurki S. Etiology of childhood pneumonia: serologic results of a prospective, population based study. Pediatr Infect Dis J 1998; 17: 986–91
9. Zangwill K, Vadheim C, Vannier A, Hemenway LS, Greenberg DP, Ward JI. Epidemiology of invasive pneumococcal disease in southern California: implications for the design and conduct of a pneumococcal conjugate vaccine efficacy trial. J Infect Dis 1996; 174: 752–9
10. Laurichesse H, Grimaud O, Waight P, Johnson A, George R, Miller E. Pneumococcal bacteraemia and meningitis in England and Wales, 1993 to 1995. Comm Dis Publ Health 1998; 1: 22–7
11. Teele DW, Klein JO, Rosner B. Epidemiology of otitis media during the first seven years of life in children in Greater Boston: a prospective, cohort study. J Infect Dis 1989; 160: 83–94
12. Bluestone C, Klein J. Otitis media in infants and children. 2nd ed. Philadelphia: WB Saunders, 1995
13. Barnett E, Klein J. The problem of resistant bacteria for the management of acute otitis media. Pediatr Clin North Am 1995; 42: 509–17
14. MMWR. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997; 46: 1–24
15. Fedson D, Musher D, Eskola J. Pneumococcal vaccine. In: Plotkin SA, Orenstein WA, eds. Vaccines. Philadelphia: WB Saunders, 1999: 553–607
16. Sell SH, Wright PF, Vaughn WK, Thompson J, Schiffman G. Clinical studies of pneumococcal vaccines in infants. I. Reactogenicity and immunogenicity of two polyvalent polysaccharide vaccines. Rev Infect Dis 1981; 3: S97–S107
17. Douglas R, Paton J, Duncan S, Hansman D. Antibody response to pneumococcal vaccination in children younger than five years of age. J Infect Dis 1983; 148: 131–7
18. Appelbaum P. Antimicrobial resistance in Streptococcus pneumoniae: an overview. Clin Infect Dis 1992; 15: 77–83
19. Song J-H, Lee NY, Ichiyama S, Yoshida R, Hirakata Y, Fu W, Chongthaleong A, Aswapokee N, Chiu CH, Lalitha MK, Thomas K, Perera J, Yee TT, Jamal F, Warsa UC, Vinh BX, Jacobs MR, Appelbaum PC, Pai CH. Spread of drug-resistance Streptococcus pneumoniae in Asian countries: Asian network for surveillance of resistant pathogens (ANSORP) study. Clin Infect Dis 1999; 28: 1206–11
20. Siber G. Pneumococcal disease: prospects for a new generation of vaccines. Science 1994; 274: 1385–7
21. Eskola J, Anttila M. Pneumococcal conjugate vaccines. Pediatr Infect Dis J 1999; 18: 543–51
22. Steinhoff MC, Edwards K, Keyserling H, Thoms ML, Johnson C, Madore D, Hogerman D. A randomized comparison of three bivalent Streptococcus pneumoniae glycoprotein conjugate vaccines in young children: effect of polysaccharide size and linkage characteristics. Pediatr Infect Dis J 1994; 13: 368–72
23. Kayhty H, Ahman H, Ronnberg PR, Tillikainen R, Eskola J. Pneumococcal polysaccharide-meningogococcal outer membrane protein complex conjugate vaccine is immunogenic in infants. J Infect Dis 1995; 172: 1273–8
24. Leach A, Ceesay SJ, Banya WAS, Greenwood B. Pilot trial of a pentavalent pneumococcal polysaccharide/protein conjugate vaccine in Gambian infants. Pediatr Infect Dis J 1996; 15: 333–9
25. Dagan R, Melamed R, Muallem M, Piglansky L, Greenberg D, Abramson O, Mendelman PM, Bohidar N, Yagupsky P. Reduction of nasopharyngeal carriage of pneumococci during the second year of life by a heptavalent conjugate pneumococcal vaccine. J Infect Dis 1996; 174: 1271–8
26. Anderson EL, Kennedy DJ, Geldmacher KM, Donnelly J, Mendelman PM. Immunogenicity of heptavalent pneumococcal conjugate vaccine in infants. J Pediatrics 1997; 128: 649–53
27. Obaro SK, Huo Z, Banya WA, Henderson DC, Monteil MA, Leach A, Greenwood BM. A glycoprotein conjugate vaccine

primes for antibody responses to a pneumococcal polysaccharide vaccine in Gambian children. Ped Infect Dis J 1997; 16: 1135–40
28. Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP. Immunogenicity and impact on nasopharyngeal carriage of a nonvalent pneumococcal conjugate vaccine. J Infect Dis 1999; 180: 1171–6
29. Butler J, Breiman R, Lipman H, Hofmann J, Facklam R. Serotypes distribution of Streptococcus pneumoniae infections among preschool children in the United States, 1978–1994: implications for development of a conjugate vaccine. J Infect Dis 1995; 171: 885–9
30. Hausdorff WP, Bryant J, Kloek C, Paradiso PR, Siber GR. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, part II. Clin Infect Dis 2000; 30: 122–40
31. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, Elvin L, Ensor KM, Hackell J, Siber G, Malinoski F, Madore D, Chang I, Kohberger R, Watson W, Austrian R, Edwards K. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000; 19: 187–95
32. Dagan R, Givon-Lavi N, Shkolnki L, Yagupsky P, Fraser D. Acute otitis media caused by antibiotic-resistant Streptococcus pneumoniae in Southern Israel: implication for immunizing with conjugate vaccines. J Infect Dis 2000; 181: 1322–9
33. Sniadack DH, Schwartz B, Lipman H, Bogaerts J, Butler JC, Dagan R, Echaniz-Aviles G, Lloyd-Evans N, Fenoll A, Girgis NI, et al. Potential interventions for the prevention of childhood pneumonia: geographic and temporal differences in serotype and serogroup distribution of sterile site pneumococcal isolates from children—implications for vaccine strategies. Pediatr Infect Dis J 1995; 14: 503–10
34. Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, Takala A, Kayhty H, Karma P, Kohbert Kohberger R, Siber G, Makela PH, for the Finnish Otitis Media Study Group. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. NEJM 2001; 344: 403–9.
35. Black S, Shinefiled H. Efficacy of heptavalent conjugate pneumococcal vaccine (Wyeth Lederle) in 37000 infants and children: impact on penumonia, otitis media, and an update on invasive disease. Results of the Northern California Kaiser Permanente Efficacy Trial. 39th Interscience Conference on Antimicrobial Agents Chemotherapy Conference (ICAAC). San Francisco, CA: 1999
36. Ahman H, Kayhty H, Tamminen P, Vuorela A, Malinoski F, Eskola J. Pentavalent pneumococcal oligosaccharide conjugate vaccine PncCRM is well tolerated and able to induce an antibody response in infants. Pediatr Infect Dis J 1996; 15: 134–9
37. King JC, Vink PE, Farley JJ, Parks M, Smilie M, Madore D, Lichenstein R, Malinoski F. Comparison of the safety and immunogenicity of a pneumococcal conjugate vaccine with a licensed polysaccharide vaccine in human immunodeficiency virus and non-human immunodeficiency virus infected children. Pediatr Infect Dis J 1996; 15: 192–6
38. King JC, Vink PE, Farley JJ, Smilie M, Parks M, Lichenstein R. Safety and immunogenecity of three doses of a five-valent pneumococcal conjugate vaccine in children younger than two years with and without human immunodeficiency virus infection. Pediatrics 1997; 99: 575–80
39. Chan CY, Molrine DC, George S, Tarbell NJ, Mauch P, Diller L, Shamberger RC, Phillips NR, Goorin A, Ambrosino DM. Pneumococcal conjugate vaccine primes for antibody responses to polysacharide pneumococcal vaccine after treatment of Hodgkin's disease. J Infect Dis 1996; 173: 256–8
40. Sarnaik S, Kaplan J, Schiffman G, Bryla D, Robbins J, Schneerson R. Studies on pneumococcus vaccine alone or mixed with DTP and a pneumococcus type 6B and Haemophilus influenzae type b capsular polysaccharide tetanus toxoid conjugates in two- to five-year-old children with sickle cell anemia. Pediatr Infect Dis J 1990; 9: 181–6
41. Vernacchio L, Neufeld EJ, MacDonald K, Kurth S, Murakami S, Hohne C, King M, Molrine D. Combined schedule of 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal vaccine in children and young adults with sickle cell disease. J Pediatr 1998; 133: 275–8
42. Obaro S, Adegbola R, Banya W, Greenwood B. Carriage of pneumococci after pneumococcal vaccine. Lancet 1996; 348: 271–2
43. Riley ID, Douglas RM. An epidemiologic approach to pneumococcal disease. Rev Infect Dis 1981; 3: 233–5
44. Shahid N, Steinhoff M, Hoque S, Begum T, Thompson C, Siber GR. Serum, breast milk, and infant antibody after maternal immunisation with pneumococcal vaccines. Lancet 1995; 346: 1252–7
45. O'Dempsey T, McArdle T, Ceesay S, Banya W, Demba E, Secka O, et al. Immunisation with a pneumococcal capsular polysaccharide vaccine during pregnancy. Vaccine 1996; 14: 963–70
46. Siber GR, Thompson C, Reid GR, Almeido-Hill J, Zacher B, Wolff M, Santosham M. Evaluation of bacterial polysaccharide immune globulin for the treatment or prevention of Haemophilus influenzae type b and pneumococcal disease. J Infect Dis 1992; 16: S129–S33
47. Lieu TA, Ray GT, Black SB, Butler JC, Klein JO, Breiman RF, et al. Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children. JAMA 2000; 283: 1460–8
48. Miller M. An assessment of the value of Haemophilus influenzae type b conjugate vaccine in Asia. Pediatr Infect Dis J 1998; 17: S152–S9
49. Global programme for vaccines and immunization (GPV). The WHO position paper on haemophilus influenzae type b conjugate vaccines. Weekly Epidemiol Record 1998; 73: 64–71

Received Aug. 15, 2000; revision received Dec. 27, 2000; accepted Jan. 26, 2001

Breaking the vicious circle

Moe H Kyaw[1,2], Harry Campbell[1], Ian G Jones[2],
[1]Public Health Sciences, University of Edinburgh, Edinburgh, [2]Scottish Centre for Infection and Environmental Health, Glasgow

The pneumococcus is an important cause of bacteraemia, meningitis, pneumonia, otitis media and sinusitis in children and adults. It is a major cause of morbidity and mortality, particularly in young children and in adults with underlying medical conditions.[1] The burden of pneumococcal disease is highest in infants and young children.

The World Health Organisation has conservatively estimated that in developing countries alone, each year, pneumococci are responsible for at least 1.2 million deaths in children under five years of age.[2]

Treatment for pneumococcal disease is becoming more complex due to the global increase in incidence of drug-resistant pneumococci. The prevalence of penicillin-resistant pneumococcal isolates has been reported to be 43 per cent in South Africa, 49 per cent in US, 53 per cent in France, 60 per cent in Spain, and 79 per cent in Korea.[3] Although the UK has a low level of penicillin-resistant pneumococci, an increase in penicillin-resistant invasive pneumococcal isolates from 4.2 per cent in 1992 to 12.6 per cent in 1999 have been documented recently.[4]

Recent studies have shown that patients infected with penicillin non-susceptible pneumococcal strains have longer durations of hospital stay and higher case-fatality rates than those infected with penicillin susceptible strains.[5,6] Therefore, effective measures against pneumococcal disease are of high public health priority.

Serotype distribution

The pneumococcus has at least 90 different serotypes, according to antigenic differences in their capsular polysaccharide.[8] The polysaccharide capsule is the most important virulence factor and protects the organism from phagocytosis. Worldwide data on pneumococcal serotype distribution have shown that most of pneumococcal disease is caused by 23 serotypes in adults,[8] and in children 80 per cent are caused by 7 serotypes.[10]

The five most common serotypes (6, 14, 18, 19, and 23) are responsible for global antibiotic resistance. Individual serotypes vary in their immunological properties.[9] This presents a major challenge for developing effective vaccines.

Immunisation against pneumococcal disease has been available in the UK since 1979. The current 23-valent polysaccharide vaccine covers approximately 90 per cent of invasive pneumococcal isolates in the UK.[10] This vaccine has been reported to be between 57 and 84 per cent effective against invasive pneumococcal disease in immunocompetent individuals but lower in patients with particular underlying conditions.[11] However, it does not protect against non-invasive disease such as pneumonia or otitis media and does not reduce nasopharyngeal carriage.[1]

Immature immune response in children

Capsular polysaccharides are T-cell independent antigens. Infants and young children do not have mature T- and B-lymphocyte function to respond to these antigens.[12] In addition, these capsular polysaccharides do not induce long-term immunological memory. Conjugate vaccines have been developed in response to these problems. Bacterial polysaccharides are linked to protein carriers to convert them to T-cell-dependent antigens. This results in induction of immunological memory and maturation of immune response in infants, the elderly and those with immunocompromised conditions.[7,13] Conjugate vaccines have proven highly successful in reducing invasive Haemophilus influenzae type b (Hib) and group C meningococcal diseases.

Pneumococcal conjugate vaccine formulations comprise the 7 to 11 serotypes which are responsible for most disease in children in most parts of the world. A study in California conducted among 37,868 children has shown that pneumococcal conjugate vaccine is highly efficacious in preventing invasive disease with a lower efficacy against otitis media and pneumonia.[14] Otitis media as the primary endpoint for determining vaccine efficacy was also studied in 1662 Finnish children. Preliminary data indicate an efficacy of 57 per cent against vaccine serotypes.[15] These results suggest that the effect of pneumococcal conjugate vaccination in preventing invasive disease and otitis media is likely to be substantial if the vaccine is introduced into the routine childhood immunisation schedule in the UK.

Hib conjugate vaccine has been shown to prevent nasopharyngeal colonisation that results in decrease of transmission and establishment of herd immunity. Pneumococcal conjugate vaccination has also been shown to reduce nasopharyngeal colonisation.[16] A recent trial in Finland documented an increase in otitis media episodes caused by non-vaccine serotypes in conjugate vaccine recipients compared to placebo recipients.[15]

The 7- to 11-valent conjugate vaccines also include the five serotypes which are most often associated with antibiotic resistance. A decrease in antibiotic-resistant pneumococcal serotypes has been identified in children vaccinated with conjugate vaccine.[16] In addition, siblings of children who received conjugate vaccine were less likely to carry resistant serotypes than siblings of a placebo group, indicating clear herd immunity effect within families.[16]

In the California trial, a reduction of 5.3 per cent in antibiotic use was observed in pneumococcal conjugate vaccine recipients.[14] Thus pneumococcal conjugate vaccine has the potential to reduce the prevalence of pneumococcal resistant strains and the use of antibiotics. One US economic analysis suggested that routine use of pneumococcal conjugate vaccine in infants and young children is likely to be cost effective.[18]

Safety of vaccination

Pneumococcal conjugate vaccine has also been reported to be safe and immunogenic in the elderly, in patients with HIV, sickle cell disease, Hodgkin's disease, bone marrow transplant and recurrent respiratory infections, and in Alaska Natives and American Indians in the US.[19] Although efficacy has not yet been studied in these high-risk groups and the elderly, its ability to produce high-levels of antibody with immunological memory suggests pneumococcal conjugate vaccine could be beneficial in these groups. A 7-valent pneumococcal conjugate vaccine has recently been licensed by Wyeth Vaccines throughout Europe. The same vaccine has been approved throughout the US for over a year where the routine immunisation schedule is 2, 4, 6 months for primary series and 12 to 15 months for the booster dose.[19]

It appears that a significant burden of pneumococcal disease could be reduced by widespread use of pneumococcal conjugate vaccine in young children. Its potential use in high-risk adult groups requires further research but also may be of considerable importance. Systematic surveillance is necessary to monitor the distribution of pneumococcal serotypes before and after the routine use of pneumococcal conjugate vaccine, to assure vaccine formulations include the predominant serotypes associated with disease and antimicrobial resistance.

References

1. MMWR. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 1997; 46: 1-24.
2. World Health Organisation (WHO). Vaccine research and development: report of the technical review group meeting, June 9-10, 1997. Geneva: WHO, 1997:32-36.
3. Collingnon PJ, Turnidge JD. Antibiotic resistance in *Streptococcus pneumoniae*. *MJA* 2000;173: S58-S64.
4. Reacher MH, Shah A, Livermore DM *et al.* Bacteraemia and antibiotic resistance of its pathogens reported in England and Wales between 1990 and 1998: trend analysis. *BMJ* 2000; 320: 213-216.
5. Plouffe JF, Breiman RF, Facklam RR *et al.* Bacteraemia with Streptococcus pneumoniae: implications for therapy and prevention. *JAMA* 1996; 275:194-198.
6. Feikin DR, Schuchat A, Kolczak M, Barrett NL, Harrison LH, Lefkowitz L, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995-1997. *Am J Public Health* 2000; 90: 223-229.
7. Klein DL. Pneumococcal disease and the role of conjugate vaccines. *Microb Drug Resist* 1999; 5: 147-157.
8. Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, Part I. *Clinical Infect Disease* 2000; 30: 100-121.
9. Robbins J, Austrian R, Lee C *et al.* Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. *J Infect Dis* 1983; 148: 1136-1159.
10. Colman G, Cooke E, Cookson B, Cooper P *et al.* Pneumococci causing invasive disease in Britain 1982-1990. *J Med Microbiol* 1998; 47:17-27.
11. Butler J, Breiman R, Campbell J et al. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. *JAMA* 1993; 270: 1826-1831.
12. Andersson U, Bird G, Britton S. A sequential study of human B lymphocyte function from birth to two years of age. *Acta Paediatr Scand* 1981; 70: 837-842.
13. Powers D, Anderson E, Lottenbach K, Mink C. Reactogenicity and immunogenicity of a protein conjugated pneumococcal oligosaccharide vaccine in older adults. *J Infect Dis* 1996; 173: 1014-1018.
14. Black S, Shinefield H, Fireman B *et al.* Efficacy, safety and immunogenecity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* 2000; 19: 187-195.
15. Kilpi T, Kokinen J, Herva E *et al.* Effect of a heptavalent pneumococcal conjugate vaccine (Pnc-CRM) on pneumococcal acute otitis media by serotype. In: Second International Symposium of Pneumococcal Diseases. SunCity, South Africa:, 2000 (19-23 March).
16. Mbelle N, Huebner RE, Wasas AD *et al.* Immunogenicity and impact on nasopharyngeal carriage of a nonvalent pneumococcal conjugate vaccine. *J Infect Dis* 1999;180:1171-1176.
17. Dagan R. Effect of vaccine on antibiotic-resistant *Streptococcus pneumoniae* carriage and spread. In: International Symposium of Pneumococci and Pneumococcal Diseases. Sun City, South Africa: 2000 (19-23 March).
18. Lieu TA, Ray GT, Black SB *et al.* Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children. *JAMA* 2000; 283: 1460-1468.
19. MMWR. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunisation Practices (ACIP). *MMWR Rep* 2000; 49. No RR-9: 1-38.